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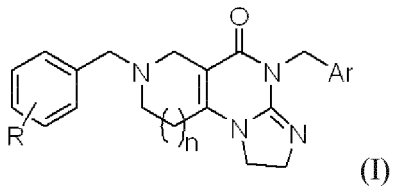
(54) IMIDAZO-PYRIMIDONE COMPOUNDS, AND PREPARATION METHOD AND APPLICATION THEREOF

(57) The present invention discloses compounds of formula (I), imidazopyrimidine ketones, wherein n, R and Ar are as described in the specifications. This invention also discloses the preparations and applications of these compounds. Whereas these compounds and pharmaceutically acceptable salts thereof can stimulate the body to produce tumor necrosis factor- related apoptosis-inducing ligands, while avoiding the drawbacks of existing cancer treatments based on recombinant proteins and antibodies. Thus, they can provide novel options for the treatment of related tumors.



(I)

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Description

Technical field

[0001] The present invention relates to the field of medical technology, in particular to imidazopyrimidinyl ketone compounds, their preparation methods and applications.

Background

[0002] As a devastating and life threatening disease, cancer has been the focus of tremendous amount of research in the past. As the result of these studies, a variety of cancer therapeutics have been developed with various degree of success. However, all traditional treatments have some limitations that cannot be ignored and more effective and safer treatments are needed by cancer patients. Recently, apoptosis-inducing molecules of tumor cells have attracted attention in the field of cancer therapy. These molecules are tumor necrosis factor-related apoptosis-inducing ligands (TRAIL), which are powerful inhibitors of cancer cells. The biggest advantage of these molecules is that they can selectively induce the apoptosis of tumor cells with no toxic side effects on normal cells. Not only can they induce the apoptosis of nearly two-thirds of tumor cell lines, but also relatively effective on tumor cells that are not sensitive to radiotherapy and chemotherapy. Therefore, TRAIL has gradually become a hot topic in cancer research since their discovery.

[0003] At present time, scientists have successfully treated cancer using tumor necrosis factor-related apoptosis-inducing ligands, which come from synthetic recombinant proteins and antibodies. Such recombinant form of soluble TRAIL has shown to induce tumor cell apoptosis. However, it can also simultaneously induce normal liver cell apoptosis. To avoid the toxic side effects, researchers have tried to obtain TRAIL by other means. U.S. Patent US2014 I 0335048A1 discloses a pharmaceutical composition for the active ingredient (7-benzyl-4-(2-methylbenzyl) 1,2,6,7,8,9-hexahydro-imidazo[1,2-a]pyrido[3,4-e]pyrimidine-5(4H)-one (TIC10), which stimulates the body to produce TRAIL while avoiding the problems of existing recombinant protein and antibody based treatments; however, there are issues regarding its applicability and activity.

Summary of the invention

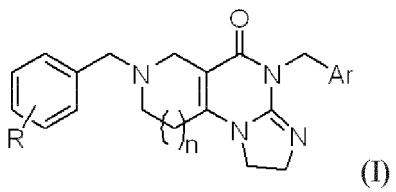
[0004] Objective of the present invention is to provide imidazole and pyrimidine ketone compounds that stimulate human TRAIL generation for the treatment of neoplastic diseases.

[0005] Another objective of the present invention is to provide methods of preparation for above compounds and pharmaceutically acceptable salts thereof.

[0006] A further objective of the present invention is to provide the above-mentioned compounds for use in the development of anti-cancer drugs.

[0007] A further objective of the present invention is to provide acceptable salts of aforementioned compounds as active ingredients in pharmaceutical compositions.

[0008] To achieve the above purpose, the technical aspects of the present invention are the preparations of the compounds of formula (I), or pharmaceutically acceptable salts thereof,



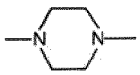
(I)

whereas, n = 0 or 1, R is H, halogen, C1-6 straight-chain or branched-chain alkyl, C1-6 straight-chain or branched-chain alkoxyl, halo-substituted C1-6 straight-chain or branched-chain alkyl, one or two hetero atoms, such as nitrogen or oxygen, an unsubstituted or substituted six-membered heterocycle alkyl; Ar is mono- or di-substituted aryl groups, the substituents include halo, C1-6 straight-chain or branched-chain alkyl, halo-substituted C1-4 straight-chain or branched-chain alkyl; and when n = 1 and R is H, Ar is not phenyl, 2-chlorophenyl, difluorophenyl or ortho-methylphenyl.

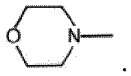
[0009] Preferably, R is H, halogen, C1-4 straight-chain or branched-chain alkyl, C1-4 straight-chain or branched-chain alkoxy, halo-substituted C1-4 straight-chain or branched-chain alkyl, one or two nitrogen hetero atoms or oxygen hetero atom, an unsubstituted or substituted six-membered heterocycle alkyl; Ar is mono- or di-substituted aryl groups, the substituents include halogen, C1-4 straight-chain or branched-chain alkyl, halo-substituted C1-4 straight-chain or branched-chain alkyl, and when n = 1 and R is H, Ar is not phenyl, 2-chlorophenyl, difluorophenyl or o-methylbenzene

group.

[0010] More preferably, R is F, Cl, Br, methyl, t-butyl, methoxy, trifluoromethyl,



or



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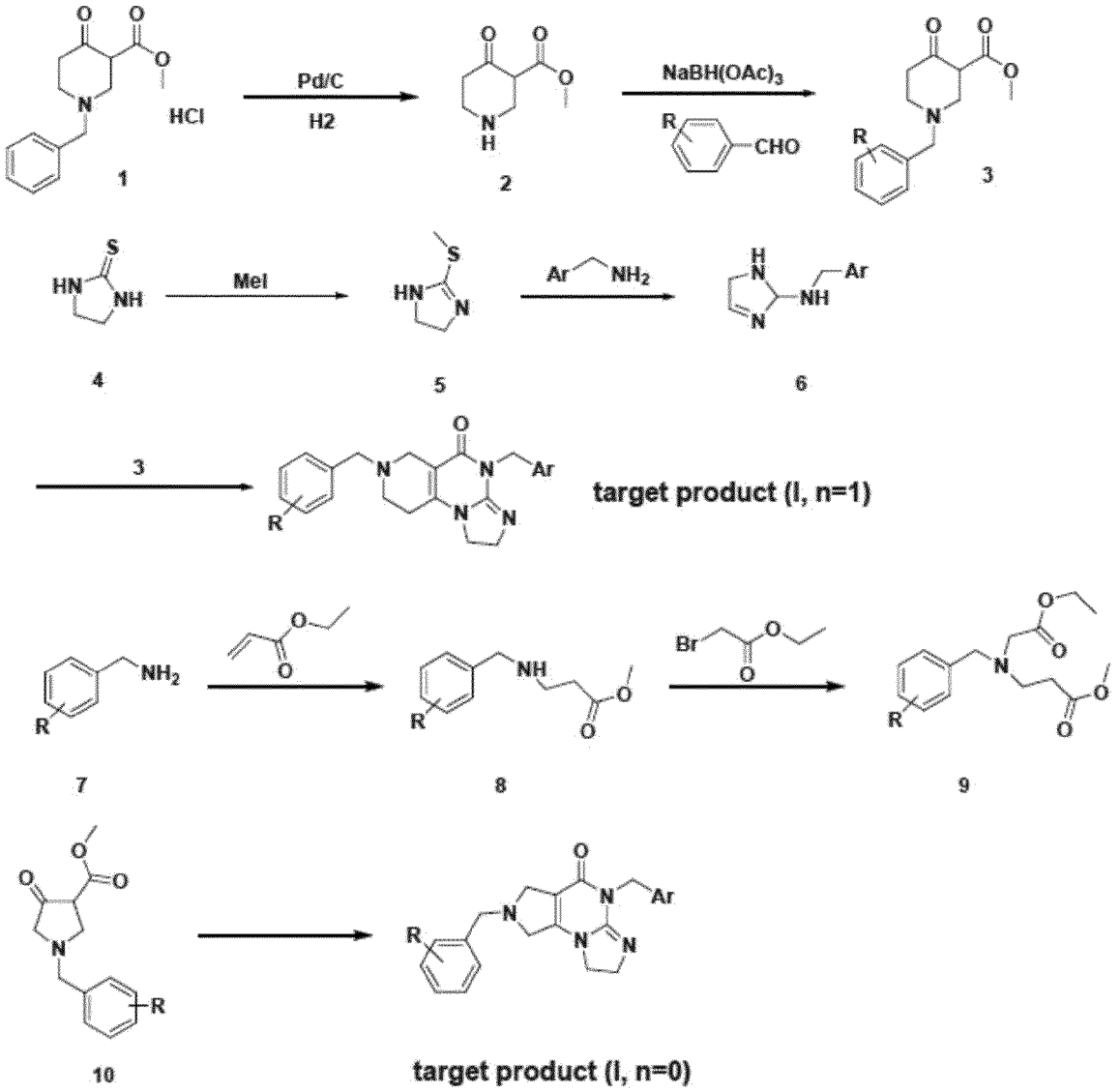
[0011] More preferably, Ar is a mono- or di-substituted aryl group, the substituent is F, Cl, one or two methyl or trifluoromethyl, or Br.

The final products in the present invention are prepared according to the following steps:

a. Compound 1 undergoes reduction reaction to obtain compound 2;
b. Compound 2 reacts with an unsubstituted or substituted benzaldehyde to prepare compound 3;
c. Compound 4 reacts with methyl iodide to prepare compound 5;
d. Compound 5 reacts with substituted benzyl amine to prepare compound 6;
e. Compound 7 reacts ethyl acrylate to prepare compound 8;
f. Compound 8 reacts with ethyl bromoacetate to prepare compound 9;
g. Compound 9 undergoes further transformation to prepare compound 10;
h. Finally, compound 10 reacts with compound 6 to give a series of compounds with n = 0; and compound 3 reacts with Compound 6 to give a series of compound with n=1.

The following reaction scheme depicts the reaction process:



[0012] Wherein R and Ar are as defined above.

[0013] Another aspect of the present invention provides a compound or a pharmaceutically acceptable salt thereof for the preparation of antitumor drugs. In particular, the tumor is colon cancer or breast cancer.

[0014] In another aspect, the present invention provides a pharmaceutical composition comprising a compound of the invention or a pharmaceutically acceptable salt thereof as an active ingredient, together with one or more pharmaceutically acceptable excipients.

[0015] The pharmaceutical compositions of the present invention comprise above-mentioned compound or a pharmaceutically acceptable salt thereof, a pharmaceutically permissible carrier mixed with pharmaceutically acceptable excipients or diluents or a combination of these compounds as active ingredients.

[0016] Said pharmaceutical composition is a pharmaceutically permissible carrier means a conventional pharmaceutical carrier in the pharmaceutical art, for example: a diluent such as water, an excipient such as starch, sucrose, etc., binders such as cellulose derivatives, alginates , gelatin, etc., humectants such as glycerin, etc., disintegrating agents such as agar-agar, calcium carbonate, calcium hydrogen carbonate, absorbents such as quaternary ammonium compounds, surface active agents such as cetyl alcohol, etc., adsorptive carriers such as kaolin and other lubricating agents such as talc, calcium stearate, magnesium stearate, and similar compound. Other adjuvants such as flavoring agents, sweeteners, etc. can also be added in the composition.

[0017] The pharmaceutical compositions of the present invention may be provided by oral, inhalation, rectal or parenteral administration mode administered to a patient in need of such treatment. For oral administration, it can be made of conventional solid preparations such as tablets, powders, granules, capsules, etc., into a liquid preparation such as water or oil suspensions, or other liquid preparations such as syrups, tinctures and the like; for parenteral, the drug can be made into a solution for injection, aqueous or oily suspensions and the like, preferably in the form of tablets, capsules

and injections.

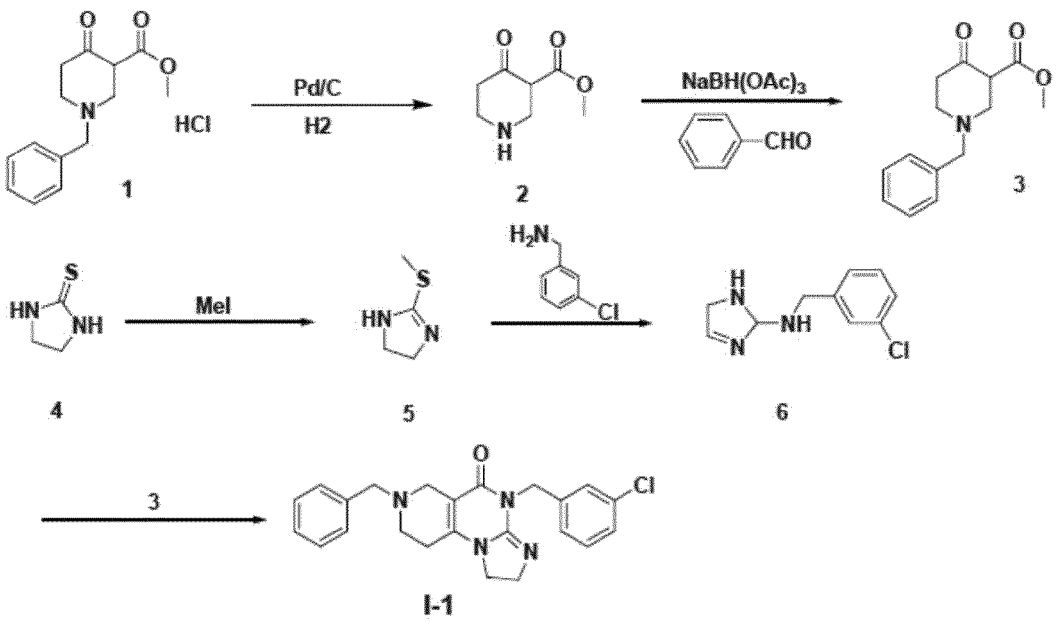
[0018] The pharmaceutical compositions of various dosage forms provided by the invention may be produced according to conventional methods for preparation of the pharmaceutical art, for example, the active ingredient is mixed with one or more carriers, and then formed into the desired dosage form.

[0019] The compounds of the present invention and their pharmaceutically acceptable salts can stimulate the body to produce tumor necrosis factor-related apoptosis-inducing ligand, thereby providing new options for treatment of related tumors.

Example 1 Synthesis of compound I-1

7-Benzyl-4-(3-chlorobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0020]



[0021] Step 1: Compound 1 (5 g, 17.7 mmol) and PdIC (500 mg) was dissolved in methanol (25 mL). The mixture was hydrogenated for 12 hours at 30 C. LCMS confirmed the reaction was completed. The PdIC was filtered off, and the filtrate was concentrated. Compound 2 was obtained (3.3 g, yield 96.5%). The product was used for next step without further purification.

[0022] Step 2: To a 50 mL three necked flask, was charged with compound 2 (1g, 5.2 mmol), 1,2 dichlorethane (10 mL), DIEA (665 mg, 5.2mmol). The mixture was stirred for 15 mixtures at 25 C. benzaldehyde (5.2 mmol) was added, followed by $NaBH(OAc)_3$ (6.7 mmol). The mixture was stirred for 2 hours at 25 C. LCMS confirmed that the reaction completed. The reaction was quenched with ice water (20 mL), extracted with dichloromethane 20 mL twice. The organic phase was combined and washed with saturated $NaHCO_3$ (25 mL), and concentrated. Compound 3 was obtained (1.22 g). The product was used for next step without further purification.

[0023] Step 3: Compound 4 (59.8 mmol) was dissolved in methanol (70 mL), CH_3I (89.7 mmol) was added dropwise at 25C. After refluxed for 30 minutes, the solvent was removed under vacuum. The residue was stirred with MTBE (50 mL), and filtered. The solid was dried under vacuum to afford compound 5 (yield 83%) as white solid.

[0024] Step 4: Compound 5 (2 mmol), and (3-chlorophenyl)methanamine (4.2 mmol) was dissolved in dioxane (5 mL) and the solution was refluxed for 12 hours. LCMS confirmed that the reaction was completed. The solvent was removed, and the residue was stirred with toluene for 12 hours. The suspension was filtered and was dried under vacuum to afford compound 6

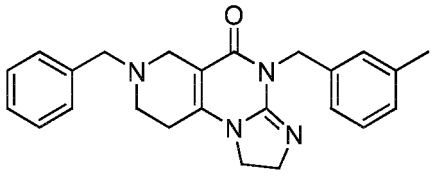
[0025] Step 5: A mixture of compound 3 (0.4mmol), compound 6 (0.4 mmol), and MeONa (1.2 mmol) in methanol (3 mL) was refluxed for 15 hours. LCMS confirmed that the reaction was completed. The reaction was cooled down to room temperature. Half of the solvent was removed under vacuum. Water (2 mL) was added dropwise. Brown solid came out, filtered and washed with water. The solid was dried under vacuum to afford I-1 (yield 25%).

^{1}HNMR ($CDCl_3$), δ 2.44 (s, 2H), 2.65 (t, J =6.4Hz, 2H), 3.29 (s, 2H), 3.65 (s, 2H), 3.87 (s, 4H), 5.01 (s, 2H), 7.19- 7.42 (m, 9H); LC-MS: m/z= 406.7(M+1).

Example 2 Synthesis of compound 1-2

7-benzyl-4-(3-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0026]



(I-2)

[0027] The procedure is same as Example 1 except:

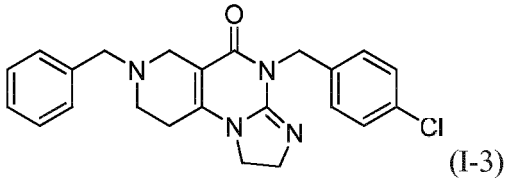
in step 4, (3-chlorophenyl)methanamine is replaced by m-tolylmethanamine.

1-2 (yield: 22%), ^{1}HNMR ($CDCl_3$), δ 2.30 (s, 3H), 2.56 (s, 2H), 2.79 (s, 2H), 3.3-3.4(m, 4H), 3.76 (s, 2H), 3.97 (m, 4H), 5.05 (s, 2H), 7.04- 7.32 (m, 9H); LC-MS: m/z= 386.8(M+1).

Example 3 synthesis of compound 1-3

7-benzyl-4-(4-chlorobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0028]



(I-3)

[0029] The procedure is same as Example 1 except:

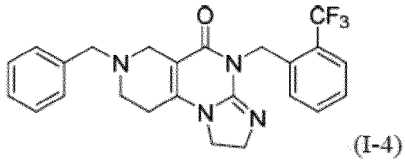
in step 4, the (3-chlorophenyl)methanamine is replaced by (4-chlorophenyl)methanamine.

1-3 (yield: 30 %), ^{1}HNMR ($CDCl_3$), δ 2.50 (s, 2H), 2.62 (t, J = 6.4Hz, 2H), 3.01 (s, 2H), 3.60 (s, 2H), 3.70 (t, J=8.8 Hz, 3H), 3.93(t, J = 8.8Hz, 2H), 4.87 (s, 2H), 7.21- 7.38 (m, 9H); LC-MS: m/z=406.7(M+1).

Example 4 synthesis of compound 1-4

7-benzyl-4-(2-(trifluoromethyl)benzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0030]



(I-4)

[0031] The procedure is same as Example 1 except:

in step 4, (3-chlorophenyl)methanamine is replaced by (2-(trifluoromethyl)phenyl)methanamine.

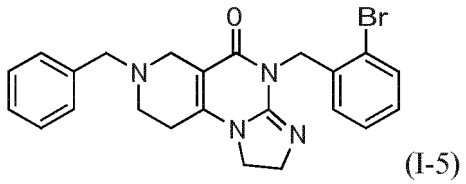
1-4 (yield: 25%), ^{1}HNMR ($CDCl_3$), δ 2.54 (s, 2H), 2.71 (s, 2H), 3.32 (s, 2H), 3.68 (s, 2H), 3.85 - 3.97 (m, 4H), 5.30 (s,

2H), 7.10 (d, J = 7.6Hz, 1H), 7.28- 7.33 (m, 6H), 7.43 (t, J = 7.6Hz, 1H), 7.63 (d, J = 7.6Hz, 1H); LC-MS: m/z= 440.7(M+1).

Example 5 synthesis of compound 1-5

7-benzyl-4-(2-bromobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0032]



(I-5)

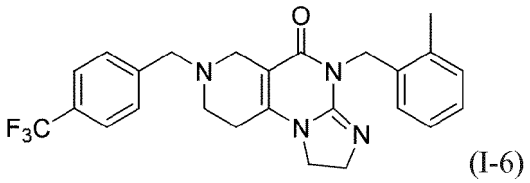
[0033] The procedure is same as Example 1 except:

in step 4, (3-chlorophenyl)methanamine is replaced by (2-bromophenyl)methanamine
1-5 (yield: 30%), ^{1}HNMR ($CDCl_3$), δ 2.49 (t, J = 5.6Hz, 2H), 2.67 (t, J = 5.6Hz, 2H), 3.31 (s, 2H), 3.66 (s, 2H), 3.81-3.91 (m, 4H), 5.11 (s, 2H), 6.97 (d, J= 8.0Hz, 1H), 7.03 (t, J= 6.4 Hz, 1H), 7.19 (t, J = 7.2Hz, 1H), 7.24- 7.32 (m, 5H), 7.51 (d, J = 8.0Hz, 1H); LC-MS: m/z= 450.6, 452.6(M+1).

Example 6 synthesis of compound 1-6

4-(2-methylbenzyl)-7-(4-(trifluoromethyl)benzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido [3,4-e]pyrimidin-5(4H)-one

[0034]



(I-6)

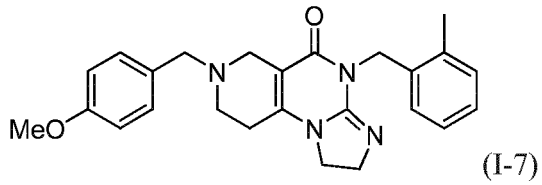
[0035] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 4-(trifluoromethyl)benzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by o-tolylmethanamine
1-6 (yield 26%), ^{1}HNMR (CD_3OD), δ 2.38 (s, 3H), 2.68 (t, J = 5.6 Hz, 2H), 2.81 (t, J = 5.6 Hz, 2H), 3.26 (s, 2H), 3.85 (m, 4H), 4.09 (t, J = 5.2Hz, 2H), 5.02 (s, 2H), 6.89 (d, J = 7.2Hz, 2H), 7.0-7.3 (m, 3H), 7.59 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H); LC-MS: m/z= 455.2(M+1).

Example 7 synthesis of compound 1-7

7-(4-methoxybenzyl)-4-(2-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0036]



(I-7)

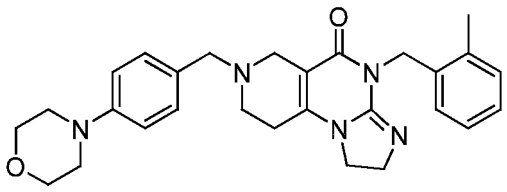
[0037] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 4-methoxybenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by o-tolylmethanamine
1-7 (yield 30%), ^{1}HNMR (CD_3OD), δ 2.38 (s, 3H), 2.70 (d, J = 5.3Hz, 2H), 2.78 (d, J = 5.3Hz, 2H), 3.23 (s, 2H), 3.66 (s, 2H), 3.80 (s, 3H), 3.84 (t, J = 8.4 Hz, 2H), 4.07 (t, J = 8.4Hz, 2H), 5.01 (s, 2H), 6.87-6.92 (m, 3H), 7.08-7.18 (m, 3H), 7.29 (t, J = 8.8Hz, 2H); LC-MS: m/z= 417.2(M+1).

Example 8 synthesis of compound 1-8

4-(2-methylbenzyl)-7-(4-morpholinobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0038]



(I-8)

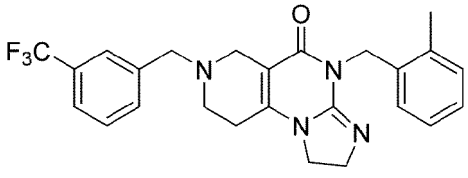
[0039] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 4-morpholinobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by o-tolylmethanamine
1-8 (yield 20%), ^{1}HNMR (CD_3OD), δ 2.37 (s, 3H), 2.61 (t, J = 5.6Hz, 2H), 2.75 (t, J = 5.6Hz, 2H), 3.13 (t, J = 4.8Hz, 4H), 3.22 (s, 2H), 3.63 (s, 2H), 3.72-3.84 (m, 6H), 4.04 (t, J = 8.8Hz, 2H), 5.00 (s, 2H), 6.88 (d, J = 7.6Hz, 1H), 6.95 (d, J =8.4 Hz, 2H), 7.07-7.17 (m, 3 H), 7.27 (d, J = 8.4 Hz, 2H); LC-MS: m/z= 472.2(M+1).

Example 9 synthesis of compound 1-9

4-(2-methylbenzyl)-7-(3-(trifluoromethyl)benzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0040]



(I-9)

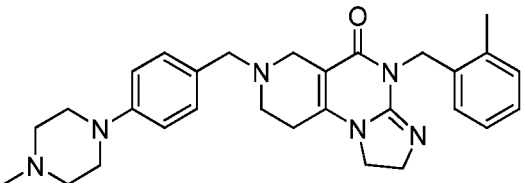
[0041] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 3-(trifluoromethyl)benzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by o-tolylmethanamine
1-9 (yield 25%), ^{1}HNMR (CD_3OD), δ 2.38 (s, 3H), 2.68 (d, J = 5.6Hz, 2H), 2.81 (t, J = 5.6Hz, 2H), 3.26 (s, 2H), 3.80 (s, 2H), 3.84 (t, J = 8.8Hz, 2H), 4.09 (t, J = 8.8Hz, 2H), 5.02 (s, 2H), 6.89 (d, J = 7.2Hz, 1H), 7.09-7.24 (m, 3H), 7.56-7.72 (m, 4 H); LC-MS: m/z= 455.2(M+1).

Example 10 synthesis of compound I-10

4-(2-methylbenzyl)-7-(4-(4-methylpiperazin-1-yl)benzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0042]



(I-10)

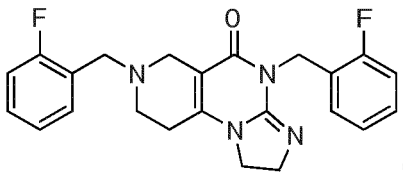
[0043] The procedure is same as Example 1 except:

in step 2: benzaldehyde is replaced by 4-(4-methylpiperazin-1-yl)benzaldehyde
in step 4: (3-chlorophenyl)methanamine is replaced by o-tolylmethanamine
1-10 (yield 19%), ^{1}HNMR (CD_3OD), δ 2.35-2.38 (m, 6H), 2.61 (s, 6H), 2.75 (t, J = 5.6Hz, 2H), 3.21 (m, 6H), 3.63 (s, 2H), 3.81 (t, J = 8.8Hz, 2H), 4.04 (t, J = 8.8Hz, 2H), 5.01 (s, 2H), 6.88 (d, J = 7.2Hz, 1H), 6.96 (d, J = 7.2Hz, 2H), 7.05-7.17 (m, 3H), 7.26 (d, J = 8.4 Hz, 2H); LC-MS: m/z=485.3(M+1).

Example 11 Synthesis of compound I-11

4,7-bis(2-fluorobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0044]



(I-11)

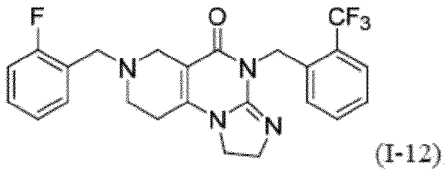
[0045] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 2-fluorobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-fluorophenyl)methanamine
I-11 (yield 25%), ^{1}HNMR (CD_3OD), δ 2.58 (t, J = 5.6Hz, 3H), 2.77 (t, J = 5.6Hz, 2H), 3.26 (s, 2H), 3.6-3.9 (m, 4H), 3.94-3.99 (m, 2 H), 5.09 (s, 2H), 7.04-7.17 (m, 6H), 7.21-7.28 (m, 2H), 7.4-7.5(m, 2H); LC-MS: m/z= 409.2(M+1).

Example 12 Synthesis of compound I-12

7-(2-fluorobenzyl)-4-(2-(trifluoromethyl)benzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0046]



(I-12)

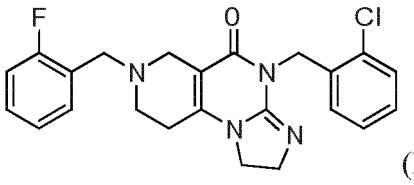
[0047] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 2-fluorobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-(trifluoromethyl)phenyl)methanamine
1-12 (yield 26%), ^{1}HNMR(DMSO_d6), δ 2.59 (s, 2H), 2.70 (t, J = 5.6Hz, 2H), 3.67 (t, J = 9.2Hz, 2H), 3.69 (s, 2H), 3.98 (t, J =9.2Hz, 2H), 5.10 (s, 2H), 7.07 (d, J =8.0Hz, 1H), 7.15-7.25 (m, 2H), 7.3-7.4 (m, 1H), 7.40-7.50 (m, 2H), 7.59 (t, J = 7.6Hz, 1H), 7.73 (d, J = 7.6Hz, 1H); LC- MS: m/z= 459.2(M+1).

Example 13 Synthesis of compound I-13

4-(2-chlorobenzyl)-7-(2-fluorobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0048]



(I-13)

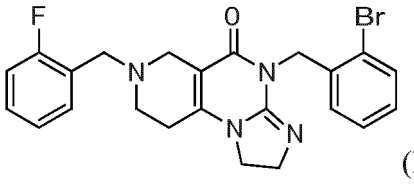
[0049] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 2-fluorobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-chlorophenyl)methanamine
1-13 (yield 30%), ^{1}HNMR(DMSO_d6), δ 2.58 (d, J = 5.6Hz, 2H), 2.69 (t, J = 5.6Hz, 2H), 3.07 (s, 2H), 3.59 (s, 2H), 3.67 (t, J = 9.2Hz, 2H), 3.98 (t, J = 9.2Hz, 2H), 4.96 (s, 2H), 6.94-6.96 (m, 1H), 7.15 (m, 3H), 7.24-7.28 (m, 2H), 7.41-7.46 (m, 2H); LC-MS: m/z= 425.1(M+1).

Example 14 Synthesis of compound I-14

4-(2-bromobenzyl)-7-(2-fluorobenzyl)-l,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0050]



(I-14)

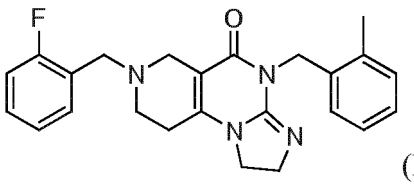
[0051] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 2-fluorobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-bromophenyl)methanamine
1-14 (yield 35%), ^{1}HNMR (CD_3OD), δ 2.58 (s, 2H), 2.68 (t, J = 5.6Hz, 2H), 3.09 (s, 2H), 3.64-3.69 (m, 4H), 3.98 (t, J =8.8Hz, 2H), 4.90 (s, 2H), 6.90 (d, J = 7.6Hz, 1H), 7.10-7.20 (m, 3H), 7.28-7.36 (m, 2H), 7.43 (t, J =7.2 Hz, 1H), 7.61 (d, J = 7.6Hz, 1H); LC-MS: m/z= 468.2, 470.2(M+1).

Example 15 Synthesis of compound I-15

7-(2-fluorobenzyl)-4-(2-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0052]



(I-15)

[0053] The procedure is same as Example 1 except:

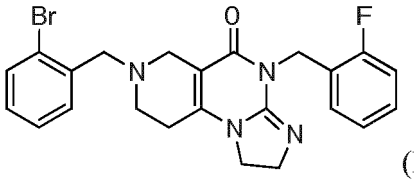
In step 2: benzaldehyde is replaced by 2-fluorobenzaldehyde

In step 4: (3-chlorophenyl)methanamine is replaced by o-tolylmethanamine
1-15 (yield 20%), ^{1}HNMR (CD_3OD), δ 2.34 (s, 3H), 2.64 (t, J = 5.6Hz, 2H), 2.77 (t, J = 5.6Hz, 2H), 3.24 (s, 2H), 3.72 (s, 2H), 3.82 (t, J = 4.8Hz, 2H), 4.6 (t, J= 4.8 Hz, 2H), 5.00 (s, 2H), 6.89 (d, J = 7.2Hz, 1H), 7.00-7.24 (m, 6H), 7.33-7.38 (m, 1H); LC-MS: m/z= 405.5(M+1).

Example 16 Synthesis of compound I-16

7-(2-bromobenzyl)-4-(2-fluorobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one:

[0054]



(I-16)

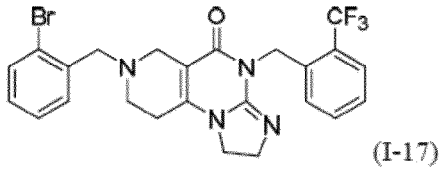
[0055] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 2-bromobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-fluorophenyl)methanamine
1-16 (yield 30%). ^{1}HNMR (CD_3OD), δ 2.61 (s, 2H), 2 .80 (t, J = 5.2Hz, 2H), 3.29 (s, 2H), 3.80 (s, 1H), 3.83 (t, J =8.8Hz, 4H), 4.03 (t, J =8.8Hz, 2H), 5.10 (s, 2H), 7.05-7.20 (m, 4H), 7.25 (t, J = 6.4Hz, 2H), 7.51 (d, J = 7.2Hz, 1H), 7.59 (d, J = 7.2Hz, 1H); LC-MS: m/z= 469.14, 470.14(M+1).

Example 17 Synthesis of compound I-17

7-(2-bromobenzyl)-4-(2-(trifluoromethyl)benzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0056]



(I-17)

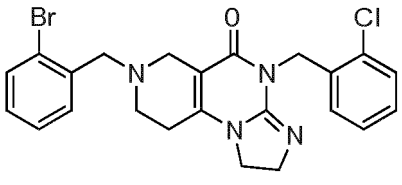
[0057] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 2-bromobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-(trifluoromethyl)phenyl)methanamine
1-17 (yield 30%), ^{1}HNMR(DMSO_d6), δ 2.61 (s, 2H), 2.74 (t, J = 5.2Hz, 2H), 3.16 (m, 2H), 3.66-3.72 (m, 4H), 4.01 (t, J = 8.8Hz, 2H), 5.11 (s, 2H), 7.09 (d, J = 7.6Hz, 1H), 7.22 (t, J = 7.6Hz, 1H), 7.39 (t, J = 6.8Hz, 1H), 7.48 (t, J = 8.8Hz, 2H), 7.61 (t, J = 7.6Hz, 2H), 7.74 (d, J =8Hz, 1H); LC-MS: m/z= 519.1(M+1).

Example 18 Synthesis of compound I-18

7-(2-bromobenzyl)-4-(2-chlorobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0058]



(I-18)

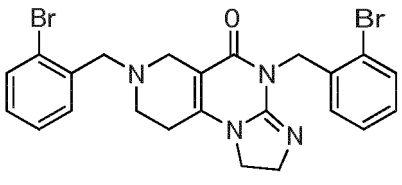
[0059] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 2-bromobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-chlorophenyl)methanamine
1-18 (yield 35%), ^{1}HNMR(DMSO_d6), δ 2.60 (t, J = 5.6Hz, 2H), 2.73 (t, J = 5.6Hz, 2H), 3.2(d, J = 8.8Hz, 2H), 3.65-3.71 (m, 4H), 4.00 (t, J= 5.2 Hz, 2H), 4.96 (s, 2H), 6.96 (t, J = 3.6Hz, 1H), 7.20-7.29 (m, 3H), 7.39 (t, J = 7.2Hz, 1H), 7.44-7.50 (m, 2H), 7.62 (d, J = 7.6Hz, 1H); LC-MS: m/z= 487.1(M+1).

Example 19 Synthesis of compound I-19

4,7-bis(2-bromobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0060]



(I-19)

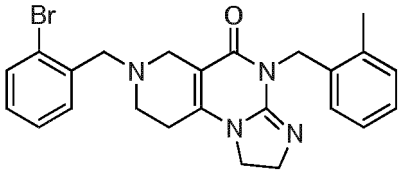
[0061] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 2-bromobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-bromophenyl)methanamine
1-19 (yield 40%), ^{1}HNMR(DMSO_d6), δ 2.50 (s, 2H), 2.73 (s, 2H), 3.14 (s, 2H), 3.60-3.71 (m, 4H), 3.99 (s, 2H), 4.91 (s, 2H), 6.91 (d, J = 5.2Hz, 1H), 7.22-7.49 (m, 5H), 7.61 (s, 2H); LC-MS: m/z= 531.1(M+1).

Example 20 Synthesis of compound 1-20

7-(2-bromobenzyl)-4-(2-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0062]



(I-20)

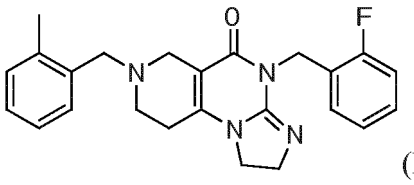
[0063] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 2-bromobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by o-tolylmethanamine
1-20 (yield 30%), ^{1}HNMR(CD_3OD), δ 2.38 (s, 3H), 2.61 (s, 2H), 2.81 (t, J = 5.2Hz, 2H), 3.32 (m, 2H), 3.78-3.83 (m, 4H), 4.02 (t, J = 9.2Hz, 2H), 5.00 (s, 2H), 6.90 (d, J = 6.8Hz, 1H), 7.05-7.20 (m, 4H), 7.34 (t, J = 6.8Hz, 1H), 7.51 (d, J= 7.6Hz, 1H), 7.59 (d, J=8.0 Hz, 1H); LC-MS: m/z= 465.1(M+1).

Example 21 Synthesis of compound 1-21

4-(2-fluorobenzyl)-7-(2-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0064]



(I-21)

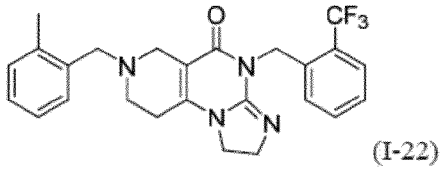
[0065] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 2-methylbenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-fluorophenyl)methanamine
1-21 (yield 20%), ^{1}HNMR(CD_3OD), δ 2.38 (s, 3H), 2.53 (t, J = 5.6Hz, 2H), 2.73 (t, J = 5.6Hz, 2H), 3.22 (s, 2H), 3.81 (m, 2H), 3.97 (m, 2H), 5.09 (s, 2H), 7.05-7.17 (m, 6H), 7.21-7.28 (m, 2H); LC-MS: m/z= 405.5(M+1).

Example 22 Synthesis of compound 1-22

7-(2-methylbenzyl)-4-(2-(trifluoromethyl)benzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0066]



(I-22)

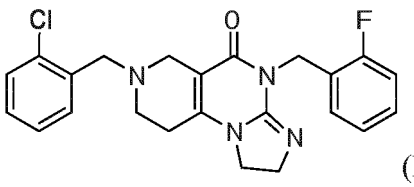
[0067] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 2-methylbenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-(trifluoromethyl)phenyl)methanamine
1-22 (yield 21%), ^{1}HNMR(DMSO_d6), δ 2.32 (s, 3H), 2.57 (s, 2H), 2.68 (t, J = 5.2 Hz, 2H), 3.06 (s, 2H), 3.59 (s, 2H), 3.67 (t, J = 9.2Hz, 2H), 3.99 (t, J = 9.2Hz, 2H), 5.10 (s, 2H), 7.07 (d, J = 8.0Hz, 1H), 7.16-7.21(m, 3H), 7.26 (d, J = 6.0Hz, 1H), 7.45 (t, J=7.6 Hz, 1H), 7.60 (t, J = 7.6Hz, 1H), 7.73 (d, J = 7.6Hz, 1H); LC-MS: m/z= 455.2(M+1).

Example 23 Synthesis of compound 1-23

7-(2-chlorobenzyl)-4-(2-fluorobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0068]



(I-23)

[0069] The procedure is same as Example 1 except:

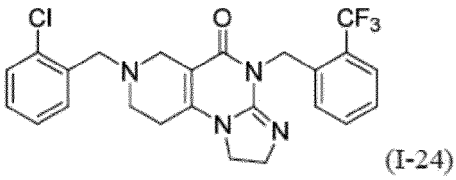
In step 2: benzaldehyde is replaced by 2-chlorobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-fluorophenyl)methanamine

1-23 (yield 22%), ^{1}HNMR(CD_3OD), δ 2.61 (s, 2H), 2.80 (t, J = 4.8Hz, 2H), 3.31 (s, 2H), 3.81 (m, 4H), 4.03 (t, J = 8.8Hz, 2H), 5.10 (s, 2H), 7.05-7.14 (m, 3H), 7.25-7.32 (m, 3H), 7.40 (d, J = 7.2Hz, 1H), 7.51 (d, J = 7.2Hz, 1H); LC-MS: m/z= 425.1(M+1).

Example 24 Synthesis of compound 1-24

7-(2-chlorobenzyl)-4-(2-(trifluoromethyl)benzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0070]



(I-24)

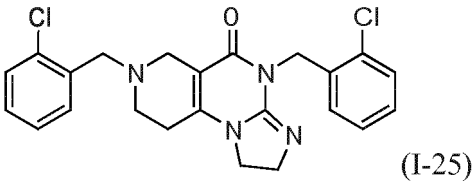
[0071] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 2-chlorobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-(trifluoromethyl)phenyl)methanamine
1-24 (yield 25%), ^{1}HNMR(DMSO_d6), δ 2.60 (s, 2H), 2.74 (t, J = 5.6Hz, 2H), 3.13 (s, 2H), 3.67 (t, J = 9.2Hz, 2H), 3.73 (s, 2H), 4.00 (t, J = 5.2Hz, 2H), 5.10 (s, 2H), 7.08 (d, J = 8.0Hz, 1H), 7.29-7.36 (m, 2H), 7.44-7.51 (m, 3H), 7.60 (t, J = 7.6Hz, 1H), 7.73 (t, J = 7.6Hz, 1H); LC-MS:m/z=475.1(M+1).

Example 25, Synthesis of compound 1-25

4,7-bis(2-chlorobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0072]



(I-25)

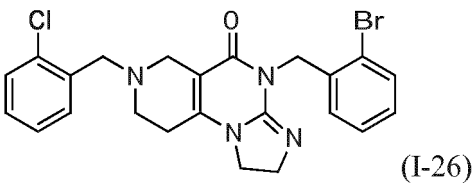
[0073] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 2-chlorobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-chlorophenyl)methanamine
1-25 (yield 28%), ^{1}HNMR(DMSO_d6), δ 2.59 (s, 2H), 2.72 (s, 2H), 3.13 (s, 2H), 3.65-3.73 (m, 4H), 3.99 (t, J = 8.4Hz, 2H), 4.96 (s, 2H), 6.96 (s, 1H), 7.27-7.34 (m, 4H), 7.44-7.51 (m, 3H); LC-MS: m/z= 441.1(M+1).

Example 26, Synthesis of compound 1-26

4-(2-bromobenzyl)-7-(2-chlorobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0074]



(I-26)

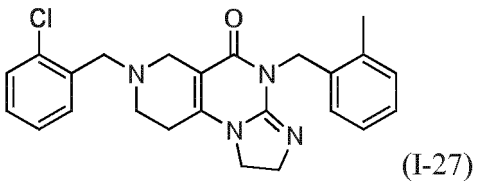
[0075] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 2-chlorobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-bromophenyl)methanamine
1-26 (yield 28%), ^{1}HNMR(DMSO_d6), δ 2.59 (s, 2H), 2.73 (t, J = 5.6Hz, 2H), 3.13 (s, 2H), 3.67 (t, J = 8.8 Hz, 2H), 3.74 (s, 2H), 3.99 (t, J = 8.8Hz, 2H), 4.91 (s, 2H), 6.91 (d, J = 7.6Hz, 1H), 7.19 (t, J = 6.8Hz, 1H), 7.30-7.36 (m, 3H), 7.43 -7.51(m, 2H), 7.62 (d, J = 8.0Hz, 1H); LC-MS: m/z= 487.1(M+1).

Example 27 Synthesis of compound 1-27

7-(2-chlorobenzyl)-4-(2-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0076]



(I-27)

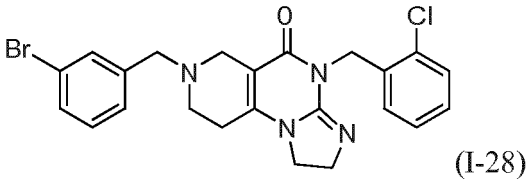
[0077] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 2-chlorobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by o-tolylmethanamine
1-27 (yield 25%), ^{1}HNMR(CD_3OD), δ 2.38 (s, 3H), 2.59 (s, 2H), 2.79 (t, J = 5.2Hz, 2H), 3.30 (s, 2H), 3.79 (m, 4H), 4.00 (t, J = 8.8Hz, 2H), 5.00 (s, 2H), 6.90 (d, J = 5.2Hz, 1H), 7.05-7.16 (m, 3H), 7.24-7.32 (m, 2H), 7.40 (d, J= 6.8Hz, 1H), 7.51 (d, J = 6.8Hz, 1H); LC-MS: m/z= 421.1(M+1).

Example 28 Synthesis of compound 1-28

7-(3-bromobenzyl)-4-(2-chlorobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0078]



(I-28)

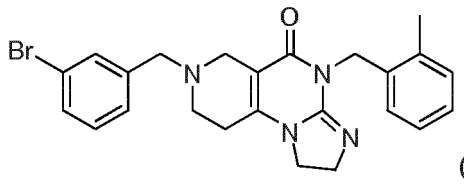
[0079] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 3-bromobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-chlorophenyl)methanamine
1-28 (yield 30%,), NMR (DMSO_d6), δ 2.58 (s, 2H), 2.65 (d, J = 4.8Hz, 2H), 3.06 (s, 2H), 3.67 (m, 4H), 3.98 (t, J = 8.8 Hz, 2H), 4.96 (s, 2H), 6.95 (t, J = 4.8Hz, 1H), 7.26-7.33 (m, 4H), 7.44-7.53 (m, 3H); LC-MS: m/z= 487.1(M+1).

Example 29 Synthesis of compound 1-29

7-(3-bromobenzyl)-4-(2-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0080]



(I-29)

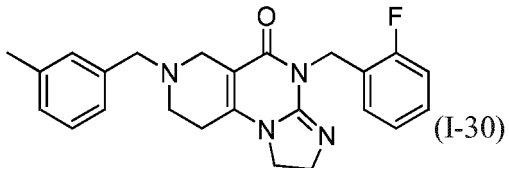
[0081] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 3-bromobenzaldehyde
In step 4: (3-chlorophenyl) methanamine is replaced by o-tolylmethanamine
1-29 (yield 38%), ^{1}HNMR (DMSO_d6), δ 2.32 (s, 3H), 2.57 (t, J = 4.8Hz, 2H), 2.65 (t, J = 4.8Hz, 2H), 3.06 (s, 2H), 3.63 (s, 2H), 3.68 (t, J = 8.8Hz, 2H), 3.97 (t, J =8.8Hz, 2H), 4.87 (s, 2H), 6.89 (d, J = 6.4Hz, 1H), 7.08-7.14 (m, 3H), 7.30-7.35 (m, 2H), 7.46 (d, J = 7.6Hz, 1H), 7.53 (s, 1 H); LC-MS: m/z= 465.1(M+1).

Example 30 Synthesis of compound 1-30

4-(2-fluorobenzyl)-7-(3-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0082]



(I-30)

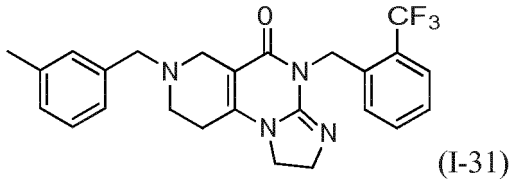
[0083] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 3-methylbenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-fluorophenyl)methanamine
1-30 (yield 25%), ^{1}HNMR(CD_3OD) δ 2.34 (s, 3H), 2.58 (s, 2H), 2.72 (t, J = 5.2Hz, 2H), 3.21 (s, 2H), 3.65 (s, 2H), 3.81 (t, J =9.2Hz, 2H), 4.00 (t, J = 9.2Hz, 2H), 5.10 (s, 2H), 7.04-7.26 (m, 8H); LC-MS: m/z= 405.2(M+1).

Example 31 Synthesis of compound 1-31

7-(3-methylbenzyl)-4-(2-(trifluoromethyl)benzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0084]



(I-31)

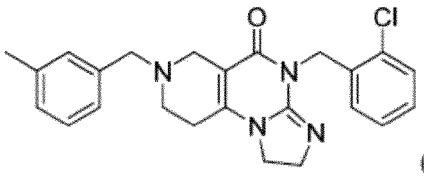
[0085] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 3-methylbenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-(trifluoromethyl)phenyl)methanamine
1-31 (yield 26%), ^{1}HNMR(DMSO_d6), δ 2.29 (s, 3H), 2.60 (t, J = 4.8Hz, 2H), 2.65 (d, J = 4.8Hz, 2H), 3.03 (s, 2H), 3.59 (s, 2H), 3.67 (t, J = 8.8Hz, 2H), 3.99 (t, J = 8.8Hz, 2H), 5.10 (s, 2H), 7.06-7.14 (m, 4H), 7.21 (t, J = 7.2Hz, 1H), 7.45 (t, J = 7.6Hz, 1H), 7.59 (t, J = 7.6Hz, 1H), 7.73 (t, J = 8.0Hz, 1H); LC-MS: m/z= 455.2(M+1).

Example 32 Synthesis of compound 1-32

4-(2-chlorobenzyl)-7-(3-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0086]



(I-32)

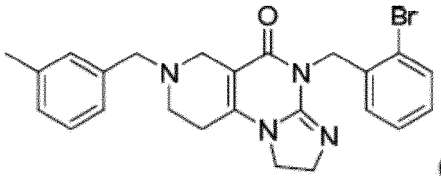
[0087] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 3-methylbenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-chlorophenyl)methanamine
1-32 (yield 26%), ^{1}HNMR(DMSO_d6), δ 2.29 (s, 3H), 2.57 (s, 2H), 2.64 (d, J = 5.2Hz, 2H), 3.04 (s, 2H), 3.58 (s, 2H), 3.67 (t, J = 9.2Hz, 2H), 3.98 (t, J =9.2Hz, 2H), 4.96 (s, 2H), 6.95 (t, J = 4.0Hz, 1H), 7.06-7.14 (m, 3H), 7.21-7.28 (m, 3H), 7.43-7.46 (m, 1H); LC-MS: m/z= 421.2(M+1).

Example 33 Synthesis of compound 1-33

4-(2-bromobenzyl)-7-(3-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0088]



(I-33)

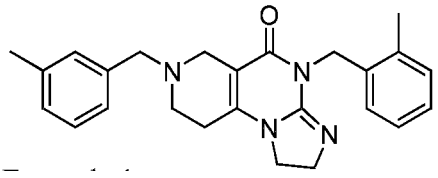
[0089] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 3-methylbenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-bromophenyl)methanamine
1-33 (yield 28%), ^{1}HNMR(DMSO_d6), δ 2.30 (s, 3H), 2.57-2.65 (m, 4H), 3.04 (s, 2H), 3.59-3.67 (m, 4H), 3.98 (s, 2H), 4.91 (s, 2H), 6.91 (s, 1H), 7.13-7.31 (m, 6H), 7.61 (s, 1H); LC-MS: m/z=466.1(M+1).

Example 34 Synthesis of compound 1-34

4-(2-methylbenzyl)-7-(3-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one:

[0090]



(I-34)

[0091] The procedure is same as Example 1 except:

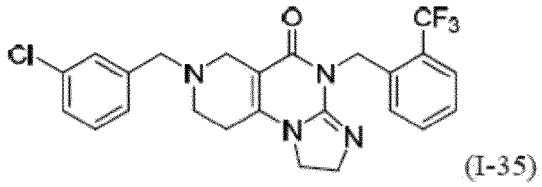
In step 2: benzaldehyde is replaced by 3-methylbenzaldehyde

In step 4: (3-chlorophenyl)methanamine is replaced by o-tolylmethanamine
1-34 (yield 22%), ^{1}HNMR(CD_3OD), δ 2.34 (s, 3H), 2.37 (s, 3H), 2.58 (d, J= 5.2Hz, 2H), 2.73 (t, J = 5.6Hz, 2H), 3.22 (s, 2H), 3.65 (s, 2H), 3.79 (t, J = 9.2Hz, 2H), 3.99 (t, J =9.2Hz, 2H), 5.00 (s, 1H), 6.89 (d, J = 3.6Hz, 1H), 7.05-7.25 (m, 7H); LC-MS: m/z= 401.2(M+1).

Example 35 Synthesis of compound 1-35

7-(3-chlorobenzyl)-4-(2-(trifluoromethyl)benzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one:

[0092]



(I-35)

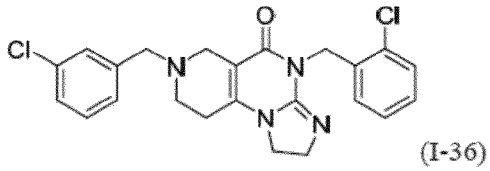
[0093] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 3-chlorobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-(trifluoromethyl)phenyl)methanamine
1-35 (yield 26%), ^{1}HNMR(DMSO_d6), δ 2.60 (s, 2H), 2.67 (d, J = 5.2Hz, 2H), 3.06 (s, 2H), 3.68 (m, 4H), 3.99 (t, J = 8.8Hz, 2H), 5.10 (s, 2H), 7.08 (d, J = 5.2Hz, 1H), 7.29-7.39 (m, 4H), 7.45 (t, J = 7.6Hz, 1H), 7.59 (t, J = 7.6Hz, 1H), 7.73(d, J = 7.6Hz, 1H); LC-MS: m/z= 475.1(M+1).

Example 36 Synthesis of compound 1-36

4-(2-chlorobenzyl)-7-(3-chlorobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0094]



(I-36)

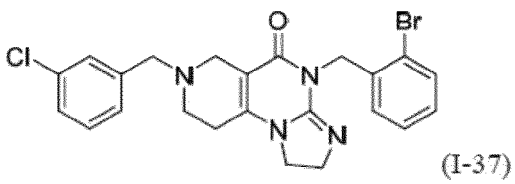
[0095] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 3-chlorobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-chlorophenyl)methanamine
1-36 (yield 28%), ^{1}HNMR(DMSO_d6), δ 2.58 (s, 2H), 2.66 (t, J = 5.2Hz, 2H), 3.07 (s, 2H), 3.67 (m, 4H), 3.99 (t, J =9.2Hz, 2H), 4.96 (s, 2H), 6.96 (t, J = 4.4Hz, 1H), 7.26-7.43 (m, 6H), 7.45 (t, J = 3.6Hz, 1H); LC-MS: m/z= 441.1(M+1).

Example 37 Synthesis of compound 1-37

4-(2-bromobenzyl)-7-(3-chlorobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0096]



(I-37)

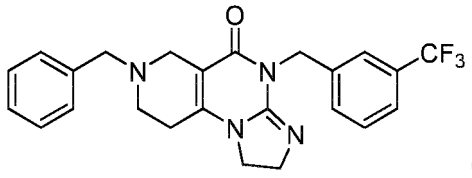
[0097] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 3-chlorobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-bromophenyl)methanamine
1-37 (yield 29%), ^{1}HNMR(DMSO_d6), δ 2.58 (s, 2H), 2.66 (t, J = 4.8Hz, 2H), 3.06 (s, 2H), 3.67 (m, 4H), 3.99 (t, J = 8.8Hz, 2H), 4.91(s, 2H), 6.91 (d, J = 7.2Hz, 1H), 7.19 (t, J = 7.2Hz, 1H), 7.29-7.39 (m, 5H), 7.61 (d, J = 7.6Hz, 1H); LC-MS: m/z= 487.1(M+1).

Example 38 Synthesis of compound 1-38

7-benzyl-4-(3-(trifluoromethyl)benzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0098]



(I-38)

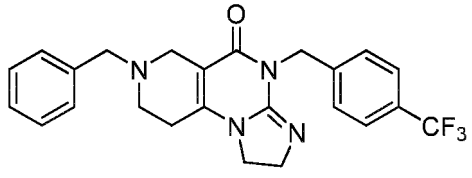
[0099] The procedure is same as Example 1 except:

In step 4: (3-chlorophenyl)methanamine is replaced by (3-(trifluoromethyl)phenyl)methanamine
1-38 (yield 20%), ^{1}HNMR(CD_3OD), δ 2.55 (t, J = 3.6Hz, 2H), 2.71 (t, J = 4Hz, 2H), 3.23 (s, 2H), 3.68 (s, 2H), 3.84 (t, J = 6.4Hz, 2H), 3.99 (t, J = 6.4Hz, 2H), 5.07 (s, 2H), 7.27 (t, 4.4Hz, 1H), 7.32- 7.37 (m, 4H), 7.47 (t, J = 5.2Hz, 1H), 7.54 (d, J = 5.2Hz, 1H), 7.61 (d, J =5.6Hz, 1H), 7.68 (s, 1H); LC-MS: m/z= 441.2(M+1).

Example 39 Synthesis of compound 1-39

7-benzyl-4-(4-(trifluoromethyl)benzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0100]



(I-39)

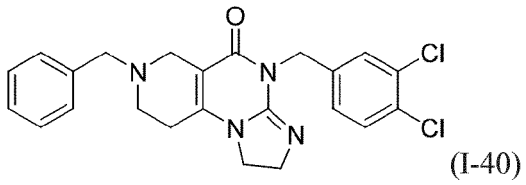
[0101] The procedure is same as Example 1 except:

In step 4: (3-chlorophenyl)methanamine is replaced by (4-(trifluoromethyl)phenyl)methanamine
1-39 (yield 18%), ^{1}HNMR(CD_3OD), δ 2.61 (t, J = 4.0Hz, 2H), 2.76 (t, J = 4.0Hz, 2H), 3.24 (s, 2H), 3.72 (s, 2H), 3.86 (t, J = 6.4Hz, 2H), 4.05 (t, J = 6.4Hz, 2H), 5.10 (s, 2H), 7.28- 7.39 (m, 5H), 7.50 (d, J = 5.2Hz, 2H), 7.60 (d, J = 5.2Hz, 2H); LC-MS: m/z= 441.2(M+1).

Example 40 Synthesis of compound 1-40

7-benzyl-4-(3,4-dichlorobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0102]



(I-40)

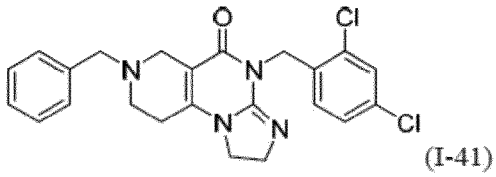
[0103] The procedure is same as Example 1 except:

In step 4: (3-chlorophenyl)methanamine is replaced by (3,4-dichlorophenyl)methanamine 1-40 (yield 20%), ^{1}HNMR(CD_3OD), δ 2.60 (s, 2H), 2.76 (s, 2H), 3.24 (s, 2H), 3.72 (s, 2H), 3.87 (t, J = 6.0Hz, 2H), 4.05 (t, J = 6.0Hz, 2H), 4.98 (s, 2H), 7.28-7.39 (m, 6H), 7.44 (d, J = 5.6Hz, 1H), 7.50 (s, 1H); LC-MS: m/z= 441.1(M+1).

Example 41 Synthesis of compound 1-41

7-benzyl-4-(2,4-dichlorobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0104]



(I-41)

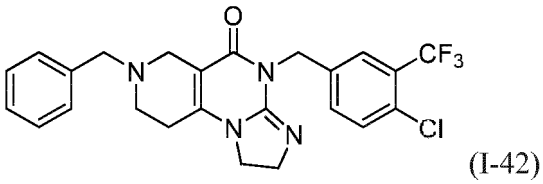
[0105] The procedure is same as Example 1 except:

In step 4: (3-chlorophenyl)methanamine is replaced by (2,4-dichlorophenyl)methanamine 1-41 (yield 19%), ^{1}HNMR(CD_3OD), δ 2.60 (s, 2H), 2.66 (t, J= 6.8Hz, 2H), 3.05 (s, 2H), 3.64 (s, 2H), 3.68 (t, J = 6.0Hz, 2H), 3.98 (t, J = 6.0Hz, 2H), 4.93 (s, 2H), 6.99 (d, J = 5.6Hz, 1H), 7.27 (d, J = 4.0Hz, 1H), 7.33-7.37 (m, 5H), 7.62 (s, 1H); LC-MS: m/z= 441.1(M+1).

Example 42 Synthesis of compound 1-42

7-benzyl-4-(4-chloro-3-(trifluoromethyl)benzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0106]



(I-42)

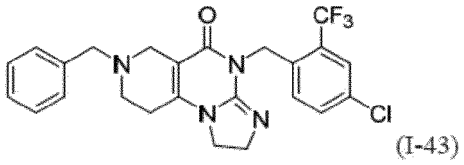
[0107] The procedure is same as Example 1 except:

In step 4: (3-chlorophenyl)methanamine is replaced by (4-chloro-3-(trifluoromethyl)phenyl)methanamine 1-42 (yield 15%), ^{1}HNMR(CD_3OD), δ 2.52 (t, J = 4.0Hz, 2H), 2.69 (d, J= 4.0Hz, 2H), 3.21 (s, 2H), 3.66 (s, 2H), 3.84 (t, J = 6.4Hz, 2H), 3.96 (t, J = 6.4Hz, 2H), 5.02 (s, 2H), 7.25-7.35 (m, 5H), 7.49 (d, J = 5.6Hz, 1H), 7.58 (d, J = 5.6Hz, 1H), 7.81 (s, 1H); LC-MS: m/z= 475.1(M+1).

Example 43 Synthesis of compound 1-43

7-benzyl-4-(4-chloro-2-(trifluoromethyl)benzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0108]



(I-43)

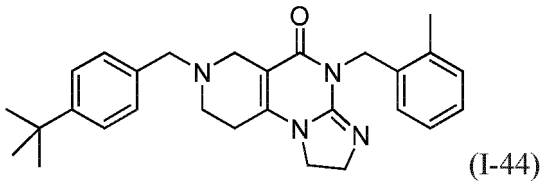
[0109] The procedure is same as Example 1 except:

In step 4: (3-chlorophenyl)methanamine is replaced by (4-chloro-2-(trifluoromethyl)phenyl)methanamine
1-43 (yield 18%), ^{1}HNMR(CD_3OD), δ 2.66 (t, J = 5.6Hz, 2H), 2.79 (t, J = 5.6Hz, 2H), 3.23 (s, 2H), 3.72 (s, 2H), 3.84 (t, J = 9.2Hz, 2H), 4.09 (t, J = 9.2Hz, 2H), 5.21 (s, 2H), 7.18 (d, J = 8.8Hz, 1H), 7.29-7.39 (m, 5H), 7.56 (d, J = 8.8Hz, 1H), 7.73 (d, J = 1.6Hz, 1H); LC-MS: m/z= 475.1(M+1).

Example 44 Synthesis of compound 1-44

7-(4-tert-butylbenzyl)-4-(2-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0110]



(I-44)

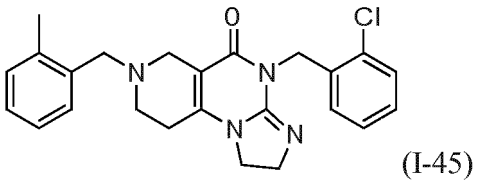
[0111] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 4-tert-butylbenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by o-tolylmethanamine
1-44 (yield 25%), ^{1}HNMR (DMSO_d6), δ 2.31 (s, 3H), 2.56 (s, 2H), 2.64 (d, J =4Hz, 2H), 3.02 (s, 2H), 3.58 (s, 2H), 3.68 (t, J = 8.8Hz, 2H), 3.97 (t, J = 8.8Hz, 2H), 4.87(s, 2H), 6.89 (d, J = 6.8Hz, 1H), 7.10 (m, 3H), 7.24 (d, J = 6.8 Hz, 2H), 7.35 (d, J= 6.8 Hz, 1H). LC-MS: m/z= 443.2(M+1).

Example 45 Synthesis of compound 1-45

4-(2-chlorobenzyl)-7-(2-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0112]



(I-45)

[0113] The procedure is same as Example 1 except:

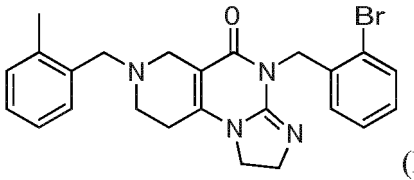
In step 2: benzaldehyde is replaced by 2-methylbenzaldehyde

In step 4: (3-chlorophenyl)methanamine is replaced by (2-chlorophenyl)methanamine
1-45 (yield 22%), ^{1}HNMR (DMSO_d6), δ 2.32 (s, 3H), 2.56 (m, 2H), 2.67 (t, J = 5.6Hz, 2H), 3.07 (s, 2H), 3.60 (s, 2 H), 3.67 (t, J = 8.4Hz, 2H), 3.98 (t, J = 9.2Hz, 2H), 4.96 (s, 2H), 6.94-6.96 (m, 1H), 7.16-7.21 (m, 3H), 7.25-7.28 (m, 3H), 7.43-7.46 (m, 1H). LC-MS:m/z= 421.1(M+1).

Example 46 Synthesis of compound 1-46

4-(2-bromobenzyl)-7-(2-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0114]



(I-46)

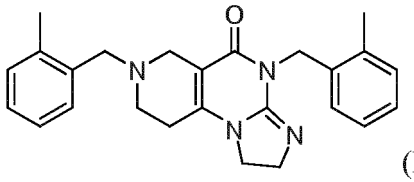
[0115] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 2-methylbenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-bromophenyl)methanamine
1-46 (yield 25%), ^{1}HNMR(DMSO_d6) δ 2.32 (s, 3H), 2.56 (s, 2H), 2.67 (t, J = 5.2Hz, 2H), 3.07 (s, 2H), 3.59 (s, 2H), 3.67 (t, J = 9.2Hz, 2H), 3.98 (t, J =9.2Hz, 2H), 4.90 (s, 2H), 6.90 (d, J = 3.6Hz, 1H), 7.13-7.33 (m, 6H), 7.61 (d, J = 8.0Hz, 1H); LC-MS: m/z= 464.1, 466.1(M+1).

Example 47 Synthesis of compound 1-47

4,7-bis(2-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0116]



(I-47)

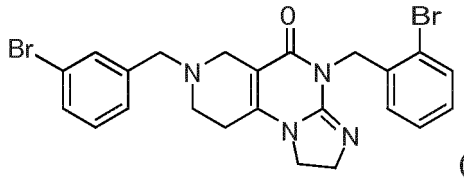
[0117] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 2-methylbenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by o-tolylmethanamine
I-47(yield 19%), ^{1}HNMR(CD_3OD) δ 2.34 (s, 3H), 2.39 (s, 3H), 2.59 (s, 2H), 2.75 (t, J = 5.2Hz, 2H), 3.24 (s, 2H), 3.67 (s, 2H), 3.80 (t, J = 9.2Hz, 2H), 4.02 (t, J = 9.2Hz, 2H), 5.00 (s, 2H), 6.89 (d, J = 7.2Hz, 1H), 7.07-7.30 (m, 7H); LC-MS:m/z= 401.2(M+1).

Example 48 Synthesis of compound 1-48

4-(2-bromobenzyl)-7-(3-bromobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0118]



(I-48)

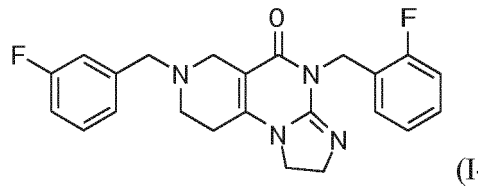
[0119] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 3-bromobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-bromophenyl)methanamine
1-48 (yield 40%), ^{1}HNMR (DMSO_d6) δ 2.59 (t, J = 4.0Hz, 2H), 2.66 (t, J = 5.2Hz, 2H), 3.06 (s, 2H), 3.67 (m, 4H), 3.98 (t, J = 9.2Hz, 2H), 4.90 (s, 2H), 6.91 (d, J = 7.2Hz, 1H), 7.20 (t, J = 6.8Hz, 1H), 7.29-7.35 (m, 3H), 7.46 (d, J = 6.8Hz, 1H), 7.54 (s, 1H), 7.62 (d, J = 7.6Hz, 1H). LC-MS: m/z= 531.0(M+1).

Example 49 Synthesis of compound 1-49

4-(2-fluorobenzyl)-7-(3-fluorobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0120]



(I-49)

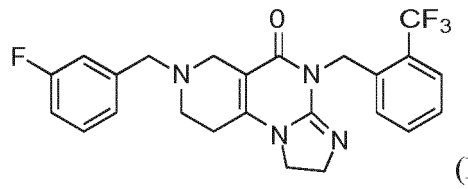
[0121] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 3-fluorobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (3-fluorophenyl)methanamine
1-49 (yield 20%), ^{1}HNMR (DMSO_d6), δ 2.56 (d, J = 4.8Hz, 2H), 2.65 (t, J = 4.8Hz, 2H), 3.06 (s, 2H) 3.65 (s, 2H), 3.69 (t, J= 9.2Hz, 2H), 3.97 (t, J = 9.2Hz, 2H), 4.96 (s, 2H), 7.07-7.18 (m, 6H), 7.26-7.29 (m, 1H), 7.35-7.39 (m, 1H); LC-MS: m/z= 409.1(M+1).

Example 50 Synthesis of compound I-50

7-(3-fluorobenzyl)-4-(2-(trifluoromethyl)benzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0122]



(I-50)

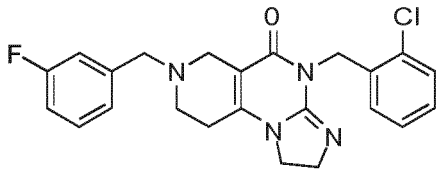
[0123] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 3-fluorobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-(trifluoromethyl)phenyl)methanamine
I-50 (yield 22%), ^{1}HNMR (DMSO_d6) δ 2.60 (t, J = 4.4Hz, 2H), 2.67 (t, J = 4.4 Hz, 2H), 3.07 (s, 2H), 3.68 (m, 4H), 34.00 (t, J = 8.8Hz, 2H), 5.10 (s, 2H), 7.07-7.18 (m, 4H), 7.35-7.47 (m, 2H), 7.60 (t, J = 7.6Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H); LC-MS:m/z= 459.1(M+1).

Example 51 Synthesis of compound I-51

4-(2-chlorobenzyl)-7-(3-fluorobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0124]



(I-51)

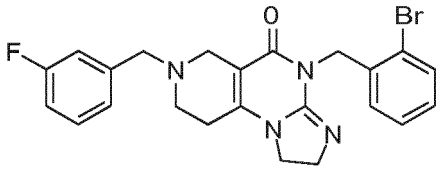
[0125] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 3-fluorobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-chlorophenyl)methanamine
I-51 (yield 30%), ^{1}HNMR(DMSO_d6) δ 2.58 (t, J = 3.6Hz ,2H), 2.67 (t, J = 5.2Hz, 2H), 3.07 (s, 2H), 3.68 (m, 4H), 3.99 (t, J = 8.8Hz, 2H), 4.96 (s, 2H), 6.94-6.96 (m, 1H), 7.07-7.18 (m, 3H), 7.25-7.29 (m, 2H), 7.35-7.46 (m, 2H); LC-MS: m/z= 425.1(M+1).

Example 52 Synthesis of compound I-52

4-(2-bromobenzyl)-7-(3-fluorobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0126]



(I-52)

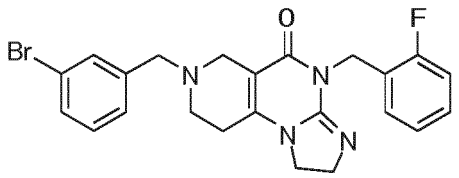
[0127] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 3-fluorobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-bromophenyl)methanamine
I-52 (yield 30%), ^{1}HNMR(DMSO_d6) δ 2.58 (s, 2H), 2.65 (t, J = 4.8Hz, 2H), 3.07 (s, 2H), 3.68 (m, 4H), 3.98 (t, J = 8.8Hz, 2H), 4.91 (s, 2H), 6.91 (d, J= 7.6Hz, 1H), 7.07-7.21 (m, 4H), 7.30-7.41 (m, 2H), 7.62 (d, J = 7.6Hz, 1H); LC-MS: m/z= 470.1(M+1).

Example 53 Synthesis of compound I-53

7-(3-bromobenzyl)-4-(2-fluorobenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0128]



(I-53)

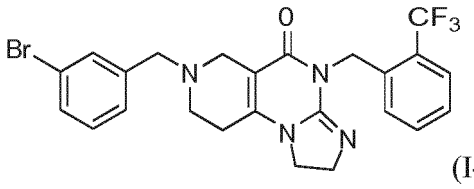
[0129] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 3-bromobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-fluorophenyl)methanamine
I-53 (yield 29%) ^{1}HNMR(DMSO_d6) δ 2.62 (t, J = 4.8Hz, 2H), 2.72 (t, J = 5.2Hz, 2H), 3.11 (s, 2 H), 3.69 (s, 2H), 3.75 (t, J=9.2 Hz, 4H), 4.03 (t, J = 9.2Hz, 2H), 5.02 (s, 2 H), 7.16-7.24 (m, 3 H), 7.34-7.40 (m, 3H), 7.52 (d, J = 7.2Hz, 1H), 7.59 (s, 1H); LC-MS:m/z= 470.1(M+1).

Example 54 Synthesis of compound I-54

7-(3-bromobenzyl)-4-(2-(trifluoromethyl)benzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one

[0130]



(I-54)

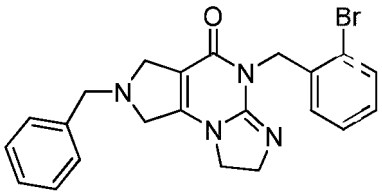
[0131] The procedure is same as Example 1 except:

In step 2: benzaldehyde is replaced by 3-bromobenzaldehyde
In step 4: (3-chlorophenyl)methanamine is replaced by (2-(trifluoromethyl)phenyl)methanamine
I-54 (yield 30%), ^{1}HNMR(DMSO_d6) δ 2.59 (s, 2H), 2.67 (t, J = 4.8Hz, 2H), 3.01 (s, 2H), 3.67 (m, 4H), 3.99 (t, J = 9.2Hz, 2H), 5.10 (s, 2H), 7.08 (d, J = 8.0Hz, 1H), 7.28-7.35 (m, 2H), 7.43-7.47 (m, 2H), 7.53 -7.61 (m, 2H), 7.73 (d, J = 7.6Hz, 1H); LC-MS: m/z= 520.1(M+1).

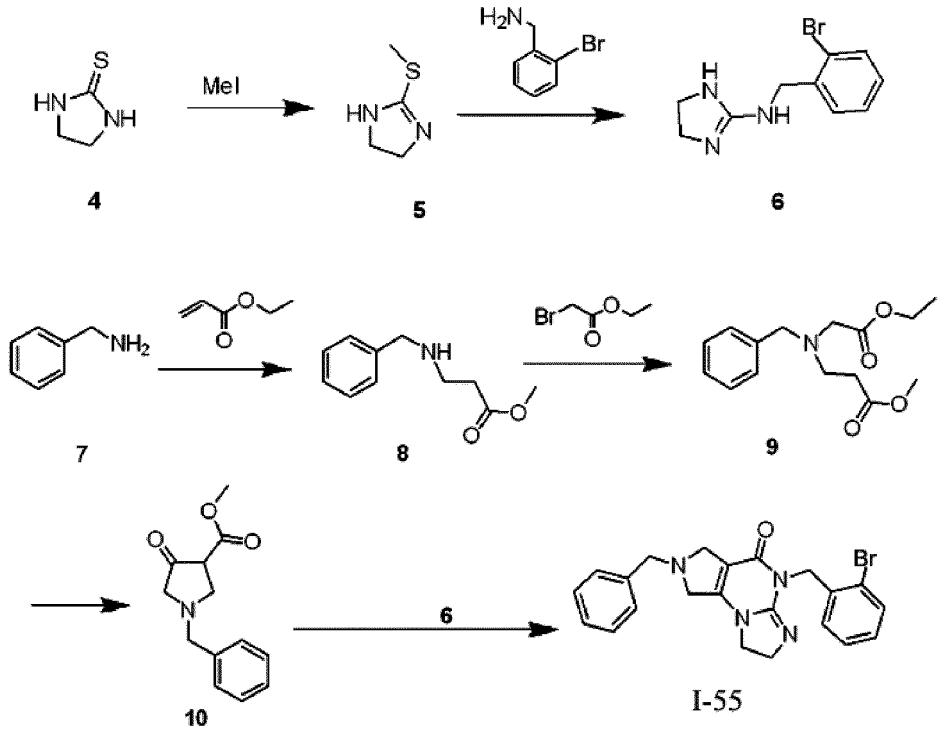
Example 55 Synthesis of compound I-55

2-Benzyl-5-(2-bromobenzyl)-2,3,7,8-tetrahydro-1H-imidazo[1,2-a]pyrrolo[3,4-e]pyrimidin-4(5H)-one

[0132]



I-55



[0133] Step1: Imidazolidine-2-thione **4**(59.8mmol) was dissolved in methanol (70ml), iodomethane (89.7mmol) was added dropwise at 25 C and the solution was refluxed for 30 minutes. The solvent was removed under vacuum, and the residue was stirred with tert-butyl methyl ether, and the suspension was filtered and the filtered cake was dried under vacuum to afford compound **5** (yield 83%).

[0134] Step 2: Compound 5 (2 mmol) was dissolved in dioxane (5 ml, and (2-bromophenyl)methanamine(4.2mmol) was added. The mixture was refluxed for 12 h. LCMS confirmed the reaction completed. The mixture was cooled down to room temperature. Solvent was removed under vacuum. The residue was stirred with toluene for 8 h. The suspension was filtered. The filtered cake was dried under vacuum to afford compound **6.**

[0135] Step 3: To a mixture of phenylmethanamine (458 mmol) and ethyl acrylate (458 mmol) in dichloromethane (500 ml, a solution of 2,2,2-trifluoroacetic acid (87.7 mmol) in dichloromethane (30 ml) was added dropwise under 10 C. The reaction was kept for 2 h at 10-15C. LC-MS confirmed the reaction was completed. The mixture was washed with saturated Na_2CO_3 solution, and the organic layer was separated, dried over Na_2SO_4, and concentrated. Compound **8** was obtained as yellow oil (85 g, 96.2%).

[0136] Step 4: To a solution of compound **8** (114.9 mmol) in acetonitrile (300 ml) K_2CO_3 (290 mmol) was added. The mixture was heated at 60 C, then ethyl 2-bromoacetate (144.6 mmol) was added dropwise. The mixture was reacted for 6 h at 60 C. LC-MS confirmed the reaction was completed. The mixture was cooled to room temperature. Dichloromethane was added, and the solution was washed with water three times. The organic layer was separated, dried over Na_2SO_4, concentrated under vacuum to afford compound 9 as yellow oil (40 g, 93.7%).

[0137] Step 5: To a solution of t-BuOK (136.6 mmol) in THF (150 ml) at -78 C under N_2, compound 9 (68.3 mmol) was added dropwise. The reaction was kept at -78 C for 3h. LC-MS confirmed that the reaction was completed. The reaction was quenched with water (300 mL), washed with ethyl acetate (150 mL) once. The aqueous layer was slowly added with NaCl until it was saturated. The system was stirred for 30 min at room temperature. White solid came out, filtered, and dried under vacuum. Compound **10** was obtained as white solid (8 g, 61.5%).

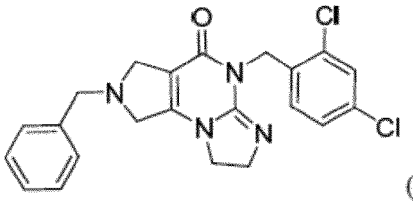
[0138] Step 6: Compound **10** (0.86 mmol) was dissolved in toluene (4 mL), compound **6** (0.9 mmol), t-BuOK (2.58 mmol) was added. The mixture was refluxed for 12h. LC-MS confirmed that the reaction was completed. The mixture was dissolved in ethyl acetate, washed with water, the organic phase was separated and concentrated. The residue was purified by TLC plate to afford desired product (10 mg, 2.7%).

^{1}HNMR (CD_3OD) δ 3.59 (m, 4H), 3.68 (s, 2H), 3.76 (t, J = 9.6 Hz, 2H), 3.92 (t, J = 9.6 Hz, 2H), 4.84 (s, 2H), 7.13-7.19 (m, 7H), 7.27-7.28 (m, 1H), 7.51 (d, J = 8.0 Hz, 1H); LC-MS: m/z= 436.1(M+1).

Example 56: Synthesis of compound I-56

2-benzyl-5-(2,4-dichlorobenzyl)-2,3,7,8-tetrahydro-1H-imidazo[1,2-a]pyrrolo[3,4-e]pyrimidin-4(5H)-one

[0139]



(I-56)

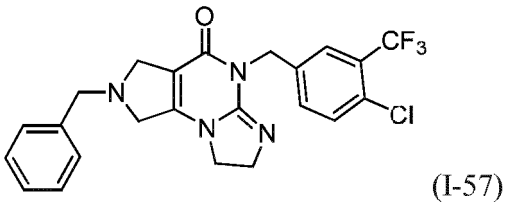
[0140] The procedure is same as Example 55 except:

In step 2: (2-bromophenyl)methanamine is replaced by (2,4-dichlorophenyl)methanamine
I-56 (yield 3.2%), ^{1}HNMR (CD_3OD) δ 3.73(m, 4H), 3.81- 3.89 (m, 4H), 4.03 (t, J = 8.4 Hz, 2H), 4.96 (s, 2H), 7.21-7.52 (m, 7H), 7.52 (d, J = 2.4 Hz, 1H); LC-MS: m/z= 427.1(M+1).

Example 57: Synthesis of compound I-57

2-benzyl-5-(4-chloro-3-(trifluoromethyl)benzyl)-2,3,7,8-tetrahydro-1H-imidazo[1,2-a]pyrrolo[3,4-e]pyrimidin-4(5H)-one

[0141]



(I-57)

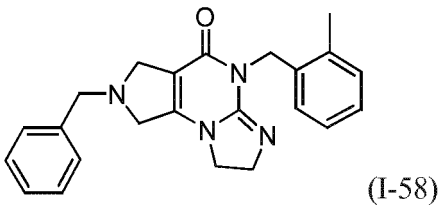
[0142] The procedure is same as Example 55 except:

In step 2: (2-bromophenyl)methanamine is replaced by (4-chloro-3-(trifluoromethyl)phenyl)methanamine
I-57 (yield 3.0%), ^{1}HNMR(CD_3OD) δ 3.69 (s, 2H), 3.78- 3.89 (m, 4H), 3.87 (m, 2H), 4.01 (m, 2H), 4.93(s, 2H), 7.25-7.33 (m, 5H), 7.51 (d, J = 8.4Hz, 1H), 7.61 (d, J = 8.4Hz, 1H), 7.70 (s, 1H); LC-MS: m/z= 461.1(M+1).

Example 58; Synthesis of compound I-58

2-benzyl-5-(2-methylbenzyl)-2,3,7,8-tetrahydro-1H-imidazo[1,2-a]pyrrolo[3,4-e]pyrimidin-4(5H)-one

[0143]



(I-58)

[0144] The procedure is same as Example 55 except:

In step 2: (2-bromophenyl)methanamine is replaced by o-tolylmethanamine
I-58 (yield 2.8%), ^{1}HNMR (CD_3OD) δ 2.26 (s, 3H), 3.65- 3.69 (m, 4H), 3.75 (s, 2H), 3.82 (t, J = 8.8 Hz, 2H), 4.01 (t,

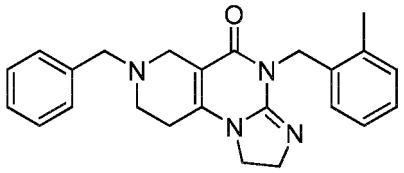
J = 8.8 Hz, 2H), 4.87 (s, 2H), 6.99 (d, J = 4.8Hz, 1H), 7.16- 7.27 (m, 8H); LC-MS: m/z= 373.2(M+1).

Comparison Example

Synthesis of TIC 10

7-benzyl-4-(2-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one (TIC10)

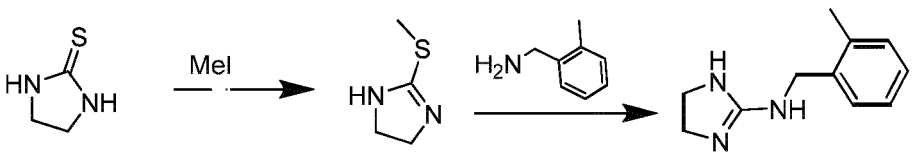
[0145]



(TIC10)

Step 1: Synthesis of N-(2-methylbenzyl)-4,5-dihydro-1H-imidazol-2-amine

[0146]



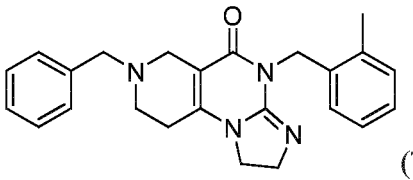
[0147] Imidazolidine-2-thione (6.93 g, 59.8 mmol) was dissolved in methanol (70 mL), iodomethane (12.9 g, 89.7 mmol) was added dropwise at 25 C. The reaction was refluxed for 30 minutes and the solvent was removed under vacuum. The residue was stirred with tert-Butyl methyl ether, filtered, and dried under vacuum to give 2-(methylthio)-4,5-dihydro-1H-imidazole (12.8g, yield 83%) as white solid.

[0148] A mixture of 2-(methylthio)-4,5-dihydro-1H-imidazole (516.2 mg, 2 mmol) and o-tolylmethanamine (508.6 mg, 4.2 mmol) in dioxane (5 mL), was refluxed for 12h, LC-MS confirmed the reaction was competed. The solvent was removed under vacuum. The residue was stirred with toluene for 8h. Then it was filtered and dried under vacuum to afford the desired N-(2-methylbenzyl)-4,5-dihydro-1H-imidazol-2-amine. LC-MS: m/z= 234.0(M+1).

Synthesis of TIC10

7-Benzyl-4-(2-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]-pyrimidin-5(4H)-one (TIC10)

[0149]



(TIC10)

[0150] Methyl 1-benzyl-4-oxopiperidine-3-carboxylate (100 mg, 0.4 mmol), N-(2-methylbenzyl)-4,5-dihydro-1H-imidazol-2-amine (128 mg, 0.4 mmol), sodium methyl alcohol (66 mg, 1.2 mmol), was dissolved in methanol (3 mL). The mixture was refluxed for 15 h under N_2. LC-MS confirmed the reaction was completed. The mixture was cooled down to room temperature. About half of solvent was removed. Water was added dropwise. Solid came out slowly. The suspension was filtered. The filtered cake was washed with water, dried under vacuum to afford TIC10(30.0 mg, yield 22.1%).

^{1}HNMR (DMSO-d6) δ 2.31 (s, 3H), 2.50-2.56 (m, 2H), 2.65 (m, 2H), 3.04 (s, 2H), 3.63-3.70 (m, 4H), 3.97 (t, J = 8.8Hz, 2H), 4.86 (s, 2H), 6.88 (d, J = 6.4Hz, 1H), 7.1-7.2 (m, 3H), 7.3-7.4 (m, 5H); LC-MS: m/z= 387.2(M+1).

Example 59 Biological Assay

[0151] The disclosed compounds and their pharmaceutically accepted salts are assayed for their anti-cancer activities by the following method.

MTS Cell Proliferation Test

1. Materials

1.1. Compounds and solvents

[0152]

Samples: the disclosed compounds
Reference compound: TIC10
DMSO was used as the solvent, Cat# 8418

1.2. Cell Lines

[0153] Two cell lines were used, both HCT116 and MDA-MB-231 were purchased from USATCC.

1.3. Reagents

[0154] MTS reagent powder was purchased from Promega. Cat# G1111; PMS from Sigma, Cat# P8625; cell culture medium RPMI-1640, Cat# 10040562R; DMEM,Cat# 10013CVR; 100x sodium pyruvate solution, Cat#136007; 100x Penicillin Streptomycin Solution, Cat# 15140122; 100x Penicillin Streptomycin Solution, Cat# 15140122; 0.25% Trypsin (Parenzyme), Cat# 25200-072; and fetal bovine serum, Cat# 16000-044 were all purchased from Life Technologies.

1.4 Instruments

[0155] Thermo incubator (Format 371);
Heat force Biosafety Cabinet (HF sage 1500);
BioTek Microplate Reader (Synergy 2).

2. Protocol

2.1 Cell Culture

[0156] HTC116 cells were cultured in DMEM complete medium
(10% FBS, 100 UlmL Penicillin, 100 ugImL Streptomycin)
MDA-MB-231 cells were cultured in RPMI-1640 complete medium (10% FBS, 100 UlmL; Penicillin, 100 μgImL; Streptomycin, 1% sodium pyruvate)

2.2 Preparation of the test solution

[0157] Solvent: DMSO
Method: the test compounds were weighed and added to DMSO at a concentration of 20 mmolIL, and stored at -80 °C. Considering the solubility of test compounds (DMSO < 1%), the following test concentrations (μmolIL) were chosen: 60, 20, 6.67, 2.22, 0.74, 0.25, 0.082, and 0.027.

2.3 Procedure of MTS methods:

[0158] Cells at logarithmic phase were harvested, then digested with 0.25% trypsin, and re-suspense in complete growth medium. 150 uLlwell of HCT-116 and MDA-MB-231 were dispensed into 96 well culture plates with 2.5 x 10^3 celllwell. The plates were pre-incubated in a humidified CO_2 incubator at 37 °C, 5% CO_2) for 24 hours. 50 uL of various concentration of test compounds and reference compound were added. A negative control (only cells and culture medium without compound) and blank control (only culture medium without cells) were set at the same time. The plates were incubated for 72 hr in the incubator. The MTSIPMS solution was prepared and added into 96 well plates according to

the test instruction by Promega Corporation. The plates were incubated again for some time, then the absorbance at 490 nm were measured using Biotek Instruments, Inc. microplate reader and the cell survival rates calculated.

$$\text{Cell Survival Rate (\%)} = (\text{At-Ab})\text{I}\ (\text{Ac-Ab}) \times 100\%$$

where,

At= Absorbance value of test compound
Ab= Absorbance value of blank
Ac=Absorbance value of control

3. Results

[0159] By using GraphPad Prism 5 software, ordinate (y): survival ratio; abscissa (x): drug concentration, the IC50 values were computed and shown in Table 1

Table 1, Assay Results (IC50: Mean ± SD)

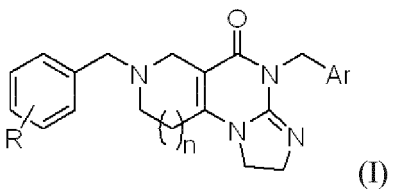
	HCT116	MDA231
No.	IC50 (Mean ± SD)	
TIC10	1.06±0.24	0.79±0.08
I-1	0.23±0.009	0.24±0.000
I-2	0.23±0.004	0.24±0.000
I-3	0.06±0.006	0.07±0.003
I-4	1.36±0.023	1.17±0.178
I-5	5.96±1.346	6.81±0.057
I-6	4.16±1.508	4.45±0.356
I-7	2.09±0.092	1.88±0.078
I-8	1.77±0.230	1.82±0.241
I-9	0.71±0.001	0.74±0.000
I-10	2.09±0.016	2.19±0.027
I-11	1.99±0.041	2.18±0.020
I-12	2.04±0.029	2.07±0.001
I-13	1.77±0.072	1.94±0.277
I-14	1.45±0.155	2.08±0.024
I-15	0.68±0.003	0.73±0.004
I-16	2.16±0.013	3.07±0.752
I-17	2.02±0.022	2.14±0.031
I-18	2.15±0.022	2.21±0.0.15
I-19	2.22±0.007	3.67±0.036
I-20	27.50±3.353	27.14±3.237
I-21	2.12±0.039	2.15±0.034
I-22	2.03±0.009	2.13±0.008
I-23	2.00±0.026	2.14±0.025
I-24	2.09±0.041	1.99±0.039

(continued)

	HCT116	MDA231
I-25	1.95±0.064	1.31±0.154
I-26	1.50±0.394	2.08±0.067
I-27	2.13±0.045	2.26±0.018
I-28	2.20±0.017	2.22±0.029
I-29	0.72±0.001	0.74±0.002
I-30	2.07±0.062	2.13±0.005
I-31	1.25±0.122	1.65±0.050
I-32	0.77±0.048	0.74±0.001
I-33	0.72±0.001	0.86±0.136
I-34	0.73±0.001	0.73±0.002
I-35	6.21±0.077	4.21±0.634
I-36	0.72±0.000	0.74±0.001
I-37	2.31±0.033	2.33±0.095
I-38	0.24 ± 0.02	0.40 ± 0.03
I-39	0.03 ± 0.00	0.05 ± 0.00
I-40	0.08 ± 0.00	0.12 ± 0.01
I-41	1.73 ± 0.25	2.01 ± 0.01
I-42	0.73 ± 0.00	1.07 ± 0.01
I-43	4.29 ± 0.21	2.85 ± 0.77
I-49	0.58±0.043	0.93±0.098
I-50	0.77±0.014	1.77±0.429
I-51	0.70±0.001	0.73±0.004
I-52	1.18±0.155	2.07±0.115
I-53	0.70±0.001	0.73±0.002
I-54	21.41±0.034	24.78±2.580
I-55	2.14±0.001	2.19±0.039
I-56	2.05 ± 0.03	2.05 ± 0.04
I-57	2.08 ± 0.01	2.10 ± 0.07

Claims

1. Compounds of formula (I), imidazole pyrimidine ketones and pharmaceutically acceptable salts thereof:

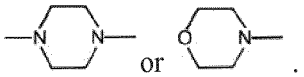


(I)

Where, n = 0 or 1;
R is H, mono- or multi halos, C1-6 straight-chain or branched-chain alkyl, C1-6 straight-chain or branched-chain alkoxy, halo-substituted C1-6 straight-chain or branched-chain alkyl, hetero substituent such as nitrogen or oxygen, six-membered heterocyclic ring with zero, one or two hetero atom substitutions.
Ar is mono- or di-substituted aryl groups, the substituent include halogen, C1-6 straight-chain or branched-chain alkyl, halo-substituted C1-6 straight-chain or branched-chain alkyl group;
And when n = 1 and R is H, Ar is not phenyl, 2-chlorophenyl, 2,4-difluorophenyl, or o-methylphenyl.

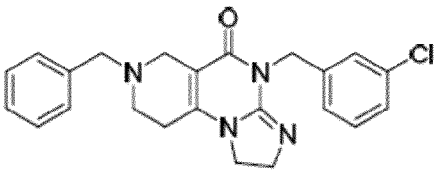
2. The compounds in claim 1 and pharmaceutically acceptable salts thereof, wherein said R is H, mono- or multi halos, C1-6 straight-chain or branched-chain alkyl, C1-6 straight-chain or branched-chain alkoxy, halo-substituted C1-6 straight-chain or branched-chain alkyl, hetero atoms such as nitrogen or oxygen, alkyl six-membered heterocyclic ring with zero, one or two hetero atom substitutions.
Ar is mono- or di-substituted aryl groups, the substituents include halogen, C1-6 straight-chain or branched-chain alkyl, halo-substituted C1-6 straight-chain or branched-chain alkyl group;
And when n = 1 and R is H, Ar is not phenyl, 2-chlorophenyl, 2,4-difluorophenyl, or o-methylphenyl.

3. The compounds in claim2 and pharmaceutically acceptable salts thereof, wherein said R is F, Cl, Br, methyl, isobutyl, methoxy, trifluromethyl,



4. The compounds in claim 2 and the pharmaceutically acceptable salts thereof, wherein, Ar is mono- or di-substituted aryl group, the substituent is one or two groups selected from F, Cl, Br, methyl or trifluoromethyl.

5. A compound or a pharmaceutically acceptable salt thereof as claimed in claim 1 wherein the compound, or a pharmaceutically acceptable salt thereof is selected from the following: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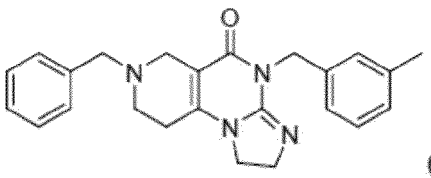
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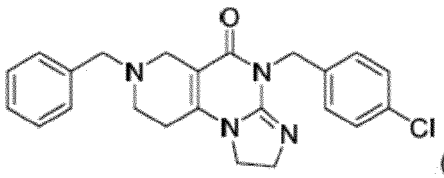
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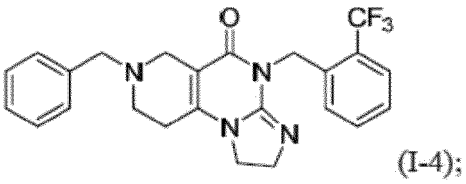
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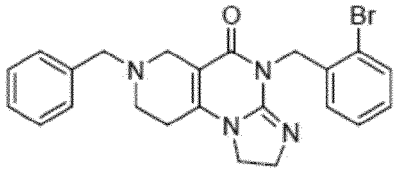
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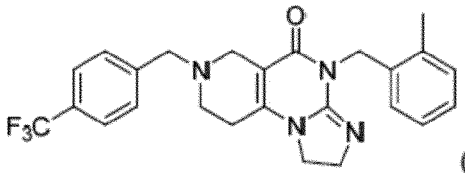
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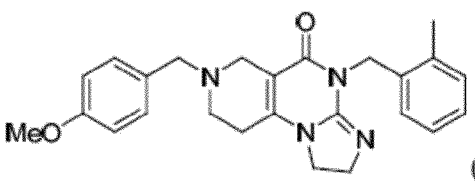
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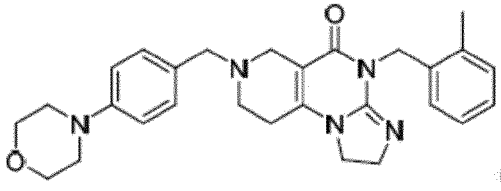
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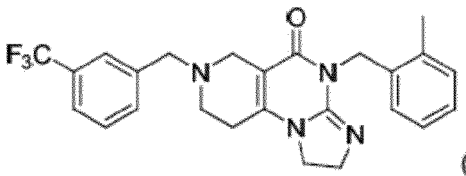
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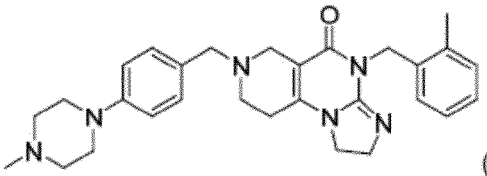
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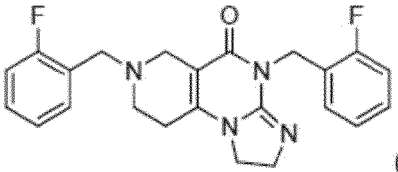
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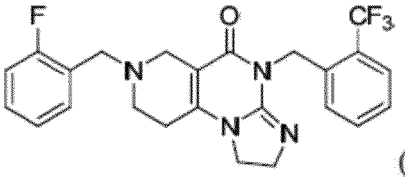
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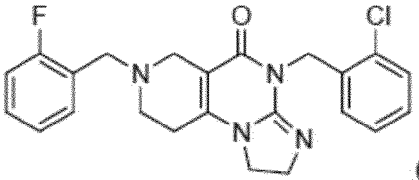
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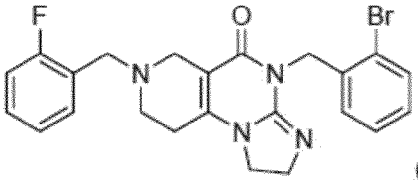
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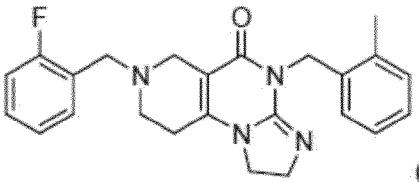
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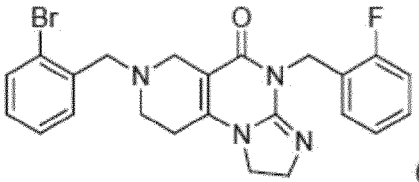
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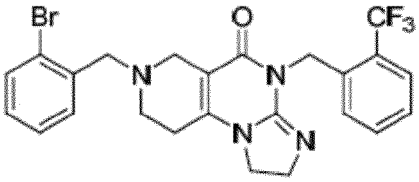
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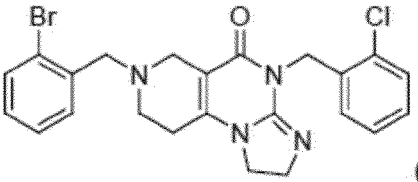
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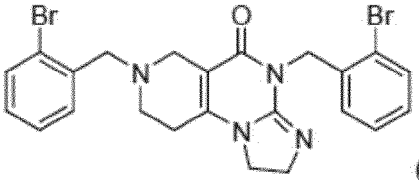
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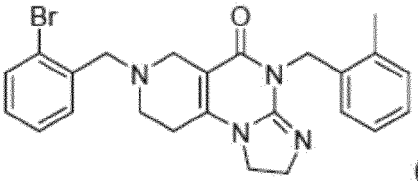
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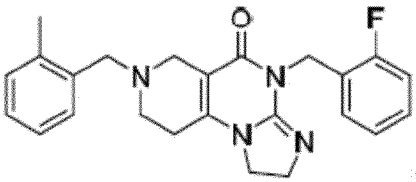
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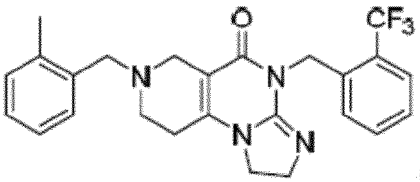
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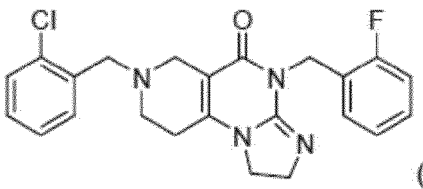
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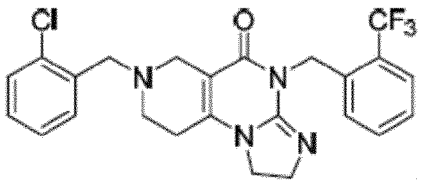
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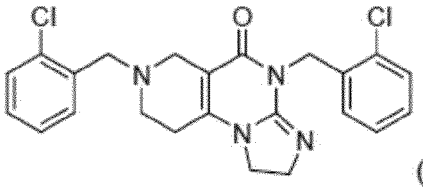
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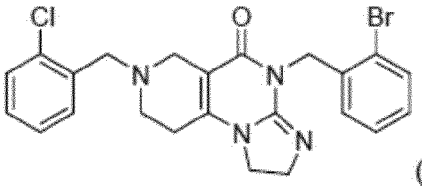
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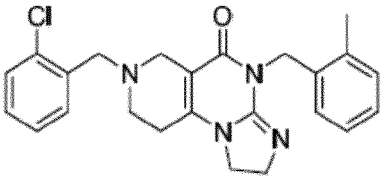
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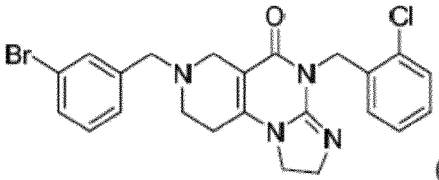
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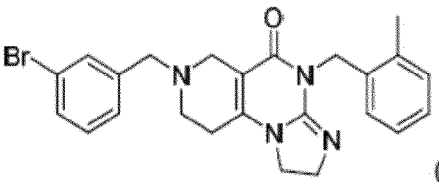
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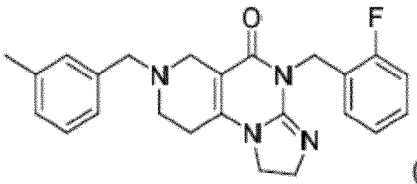
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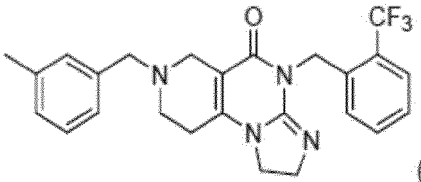
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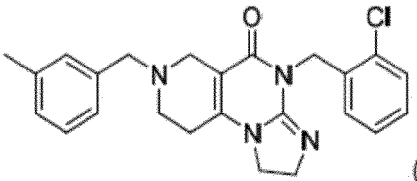
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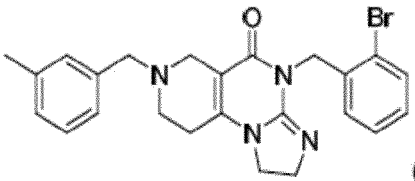
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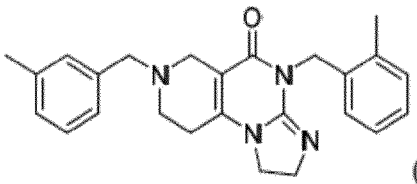
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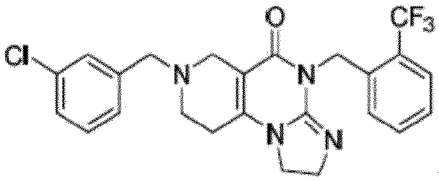
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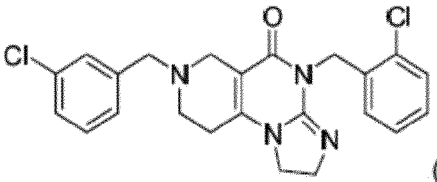
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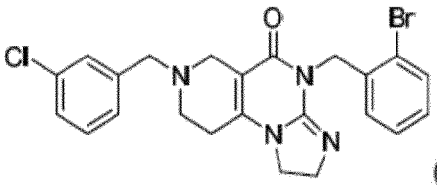
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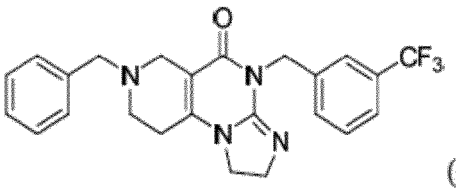
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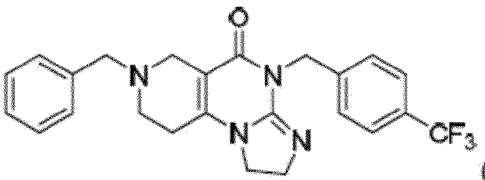
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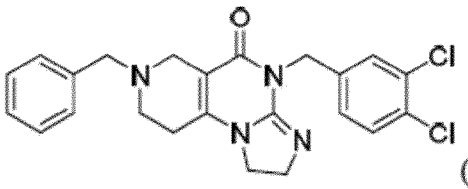
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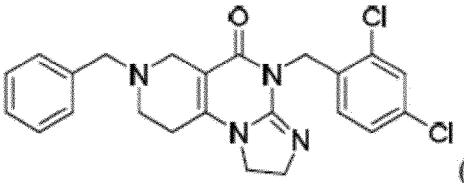
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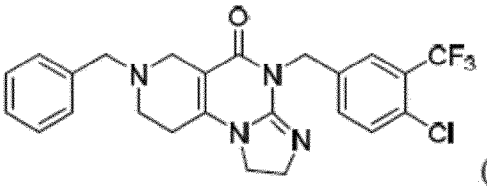
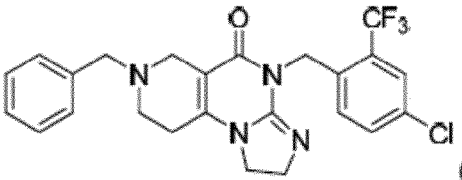
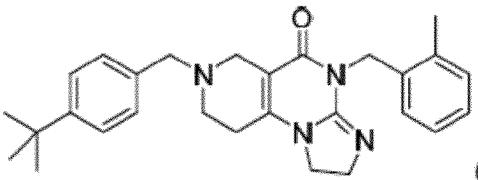
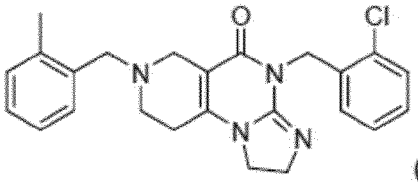
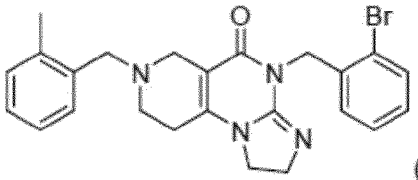
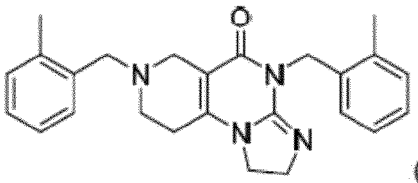

(I-42);

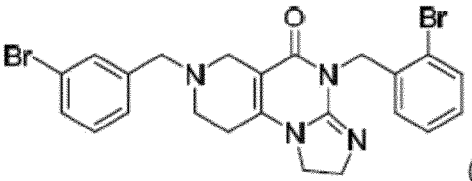

(I-43);

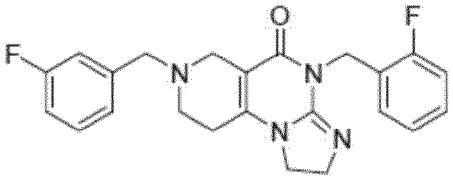

(I-44);

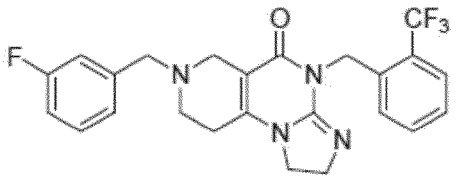

(I-45);

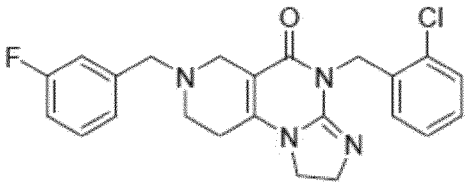

(I-46);

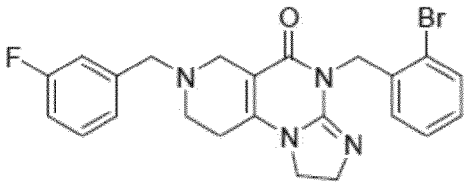

(I-47);

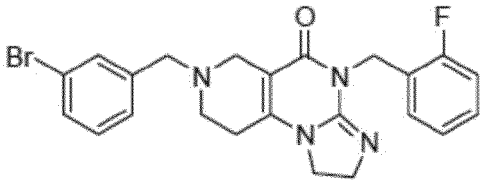

(I-48);

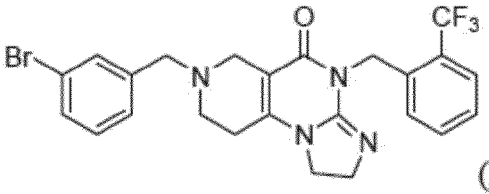

(I-49);

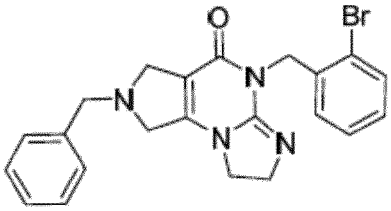

(I-50);

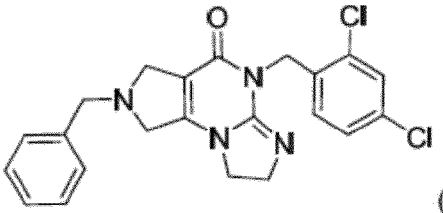

(I-51);

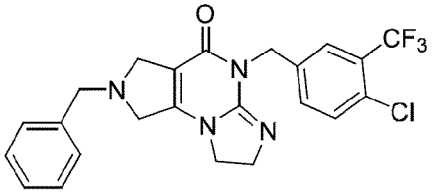

(I-52);

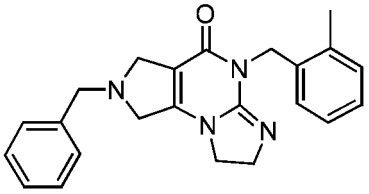

(I-53);


(I-54);

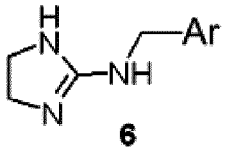

(I-55);


(I-56);


(I-57);

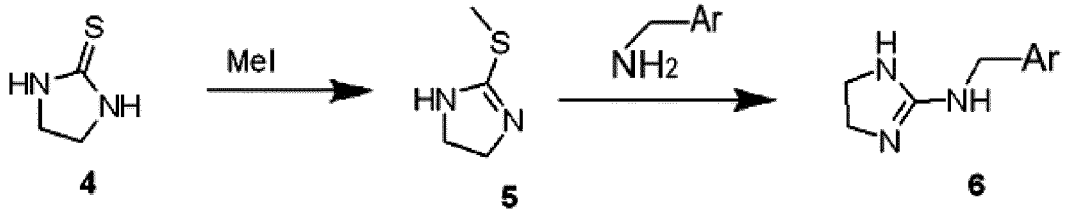

(I-58).

6. The preparation of these compounds or pharmaceutically acceptable salts thereof in any one of the preceding claims. The characteristics of the preparation is that the compound of formula (I) was prepared from the compound 6 shown below:



6

by following the reaction scheme:



4 **5** **6**

wherein Ar is as previously defined.

7. The compounds or pharmaceutically acceptable salts thereof described in any one of claims 1-5 when used as the anti-tumor agents.

8. When the compounds are used for applications according to claim 7, wherein said tumor is colon cancer or breast cancer.

9. A pharmaceutical composition that contains the compounds from claims 1-5 or pharmaceutically acceptable salts thereof as active ingredients, together with one or more pharmaceutically acceptable excipients.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2016/086145

A. CLASSIFICATION OF SUBJECT MATTER

C07D 471/14 (2006.01) i; C07D 487/14 (2006.01) i; A61P 35/00 (2006.01) i; A61K 31/5377 (2006.01) i; A61K 31/519 (2006.01) i
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CNABS, CNKI, DWPI, SIPOABS, STN (REGISTRY, CAPLUS): cancer, TNF, colon, breast, tumour, +imidazo+, +pyrimidin+, structural research based on claim 1

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	CN 104860948 A (NANJING GAITE MEDICAL TECHNOLOGY CO., LTD.), 26 August 2015 (26.08.2015), the whole document, especially claims 1-9	1-9
PX	WO 2015153468 A1 (SCRIPPS RESEARCH INSTITUDE), 08 October 2015 (08.10.2015), the whole document, especially claims 1-9	1-9
X	US 2014335048 A1 (ONCOCEUTICS INC.), 13 November 2014 (13.11.2014), description, paragraphs 0004-0005, 0012 and 0144-0150, and claim 22	1-9
X	WO 2014160130 A1 (ONCOCEUTICS INC.), 02 October 2014 (02.10.2014), the whole document	1-9

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 September 2016 (07.09.2016)	**20 September 2016 (20.09.2016)**
Name and mailing address of the ISA/CN: State Intellectual Property Office of the P. R. China No. 6, Xitucheng Road, Jimenqiao Haidian District, Beijing 100088, China Facsimile No.: (86-10) 62019451	Authorized officer **WANG, Ying** Telephone No.: (86-10) **62084463**

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2016/086145

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
CN 104860948 A	26 August 2015	None	
WO 2015153468 A1	08 October 2015	None	
US 2014335048 A1	13 November 2014	US 9376437 B2	28 June 2016
		CA 2930535 A1	21 May 2015
		AU 2014349150 A1	30 June 2016
WO 2014160130 A1	02 October 2014	JP 2016512563 A	28 April 2016
		US 9265765 B2	23 February 2016
		US 2014271540 A1	18 September 2014
		IL 241452 D0	30 November 2015
		CA 2905037 A1	02 October 2014
		CN 105530937 A	27 April 2016
		EP 2968294 A1	20 January 2016
		KR 20150136602 A	07 December 2015
		EA 201591715 A1	29 July 2016
		SG 11201507247W A	29 October 2015
		AU 2014244117 A1	08 October 2015

Form PCT/ISA/210 (patent family annex) (July 2009)

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US 2014I0335048 A1 **[0003]**